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# THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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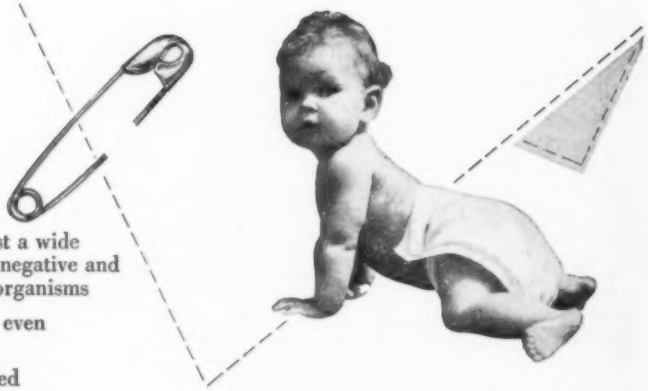

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# The Journal of Pediatrics

VOL. 43 JULY, 1953 No. 1


## BLOOD GALACTOSE IN INFANTS AND CHILDREN


ALEXIS F. HARTMANN, M.D., EDGAR GRUNWALDT, M.D., AND DAVID H. JAMES, JR., M.D.

ST. LOUIS, MO.

WITH THE TECHNICAL ASSISTANCE OF MARIE K. MORTON


IN YOUNG infants whose food is entirely milk, and especially in breast-fed babies, lactose may contribute as much as 43 per cent of the ingested calories. Since each molecule of lactose is split in the intestine into one molecule of glucose and one molecule of galactose and thus absorbed, metabolism of galactose assumes a role in early infancy almost as important as that of glucose. In comparison with the very extensive and detailed knowledge concerning the metabolism of glucose, much less is known concerning the metabolism of galactose. The following review summarizes the present state of such knowledge.

The chemical structure of naturally occurring galactose and that which is derived from lactose differs from naturally occurring glucose only at the position of $C_4$ where there is reversal of the H and OH groups (Fig. 1).

Although absorbed by the intestine at approximately the same rate as glucose,[1] galactose is metabolized less rapidly[2] and less completely,[3] especially in the dog and rabbit.[4] Its metabolism is effected chiefly, but not entirely, in the liver,[5] a fact which permits galactose utilization to be made a measure of liver function,[6, 7, 8] diffuse types of liver damage leading to higher blood concentrations and larger urinary losses than partial hepatectomy or cirrhosis. Brain tissue cannot utilize galactose directly, and galactose administration fails to relieve the symptoms of hypoglycemia. In eviscerated-nephrectomized dogs, injected galactose persists for long periods almost unchanged.[9]

During its metabolism in the liver,[10] galactose seems first to react with adenosine triphosphate (ATP) with the formation of galactose-1-$PO_4$ without demonstrable intermediary galactose 6-$PO_4$. The enzyme needed to catalyze this reaction has been called galactokinase. Transformation to glucose-1-$PO_4$ then seems to result, and from this point its metabolism must be that of glucose. For conversion of galactose-1-$PO_4$ to glucose-1-$PO_4$, an enzyme called galactowaldenase and a coenzyme thought to be uridin-diphosphate-glucose[11] are required. Which one of these two pre-


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Read before the American Pediatric Society, May 7, 1953.

liminary reactions is the factor limiting the rate of utilization of galactose is not known.

In normal rats, lactose and galactose fed in high percentage lead to cataract formation,[11] whereas controls fed other carbohydrates fail to show lenticular changes.

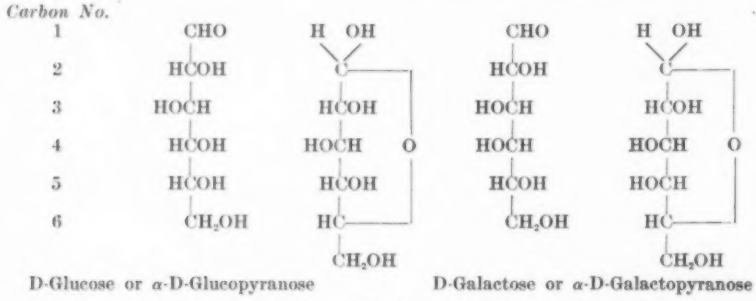


Fig. 1.

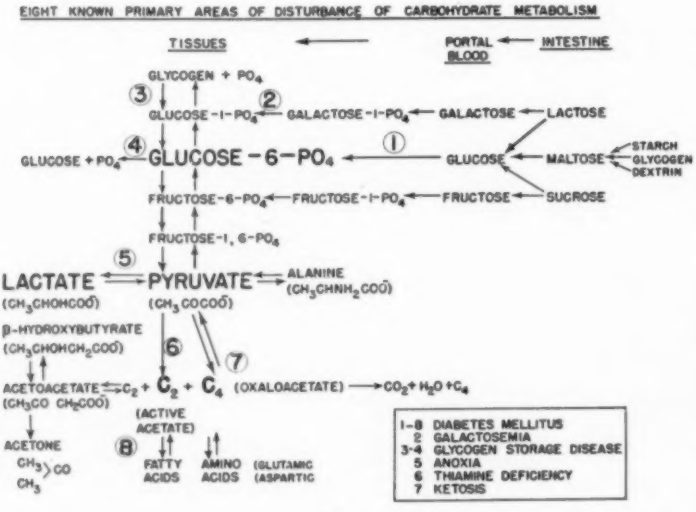


Fig. 2.

In infants with specific inability to metabolize galactose normally, severe toxic manifestations may develop if lactose is present in the diet.[12, 13, 14, 15, 16, 17] In addition to cataract formation, there are often noted nutritional and growth failure, enlargement of liver sometimes with jaundice or cirrhosis, enlargement of spleen, edema, renal changes, and mental retardation. Withdrawal of lactose from the diet often leads to spectacular improvement since many of the toxic changes are, for a while at least, reversible.

Suspicion of the presence of pathologic galactosemia is usually first entertained when urine from an infant or child with symptoms such as those described above shows a moderate amount of copper-reducing sub-

stance. Suspicion deepens when blood sugars are found only moderately elevated—to perhaps twice normal levels. Further examination should then reveal that the urinary-reducing substance is not fermented by ordinary yeast and yields mucic acid when oxidized by nitric acid and yields the characteristic osazone when treated with phenylhydrazine. The total reducing power of the blood is due to glucose plus nonyeast fermentable galactose in varying ratios. Administration of the standard test dose of galactose, 1.75 Gm. per kilogram leads to very high blood galactose values for a number of hours and to galactosuria.

The therapeutic test is the demonstration of disappearance of the galactose from the blood and urine and amelioration of symptoms when lactose is entirely removed from the diet.

During the study of an infant with typical "galactosemia," a review of the literature indicated very little knowledge of the amounts of galactose which might be present in the bloods of normal or sick infants, other than those with specific inability to metabolize the sugar. The subject seemed important enough to investigate, particularly because of the strong possibility that some cases of hypoglycemia may escape recognition because of failure to distinguish between galactose and glucose in the blood.

## METHODS

Yeast-fermentable glucose and nonfermentable galactose were determined in capillary whole blood in a number of normal or sick children and under a variety of circumstances related to feeding. Duplicate 0.2 ml. samples of blood were obtained usually from a small cut in the heel by a Bard-Parker blade. The total reducing sugar in one sample was then determined after zinc precipitation by the Somogyi modification[21] of the Shaffer-Hartmann method, the sensitive low-blank reagent[22] being used. In the duplicate sample, glucose was first removed by the following technique, strict adherence to details being necessary. Fresh baker's (Fleishmann's) yeast was purchased weekly and kept refrigerated until used. Each day a fresh suspension was prepared by washing approximately six times with distilled water, centrifuging and decanting until the wash water behaved as a distilled water blank with the copper reagent. The 0.2 ml. blood sample was added to 5.8 ml. of a 10 per cent suspension of such washed fresh yeast and allowed to stand at room temperature for five minutes before precipitation with the zinc sulfate and sodium hydroxide reagents. Shorter periods were found to give incomplete fermentation, while longer exposure either returned glucose or caused some of the galactose to disappear. With each new yeast preparation, a glucose blank of proper concentration was run in order to demonstrate complete fermentation by the technique employed. A curve of copper reduction by galactose was prepared from known concentrations of pure galactose. Except in the case of the most dilute solutions, the reducing value of galactose was found to be 0.8 that of glucose.

An unsatisfactory attempt was made to prepare in large quantity a stable galactose-adapted strain of yeast which would remove galactose as efficiently as the original yeast removed glucose. Despite failure from the quantitative viewpoint, experi-

ments with small amounts of such adapted yeast suggested little likelihood that the reducing substance left after glucose fermentation was other than galactose. Absolute identification of the nonfermentable reducing substance was, therefore, never made.

### OBSERVATIONS

From the four experiments shown in Table I the following conclusions are suggested. The patient, Shirley H., aged 2½ years, weight 7.7 kilograms, had been receiving streptomycin 0.5 Gm. b.i.d. for tuberculosis of tracheobronchial glands.

1. When a large amount (1.75 Gm. per kilogram) of galactose is fed in the absence of other food, the fasting blood sugar level approximately doubles in one hour, due entirely to rise in galactose, the true glucose actually falling slightly during this interval. Then as galactose falls during the next two hours, glucose rises to a level distinctly above the initial concentration.

2. When smaller amounts (0.2 to 0.45 Gm. per kilogram) of potential galactose are fed as cow's milk with or without added lactose, the highest galactose concentrations in the blood are again noted at approximately one hour. In two of three observations, reciprocal relationship between glucose and galactose was also observed. In the third experiment, the timing of the sampling could have masked such a relationship if it is postulated that the galactose concentration was already falling at one hour, as was actually noted to occur in Experiment 1.

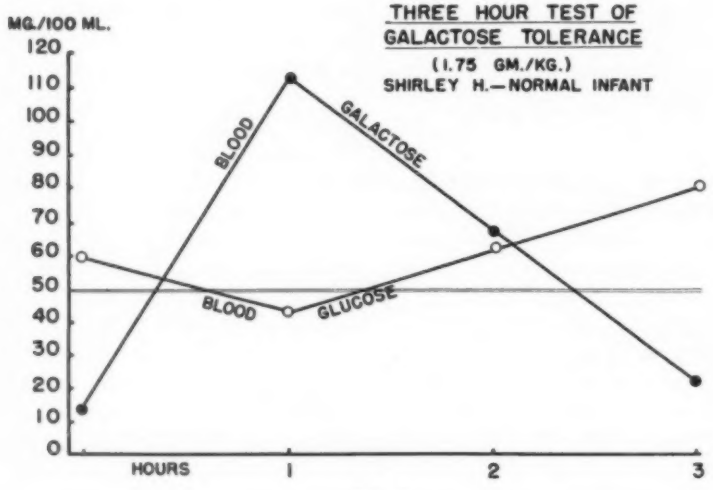


Fig. 3

3. When milk feedings are repeated every three to four hours, there are usually easily detectable quantities of galactose in the blood.

4. Under such ordinary feeding conditions galactose varies from zero

TABLE I. DETERMINATION OF THE RANGE OF GALACTOSE CONCENTRATIONS IN CAPILLARY WHOLE BLOOD IN A NORMAL OR NEARLY NORMAL INFANT RECEIVING REGULAR MILK FEEDINGS

| | TOTAL SUGAR | | REMOVED BY YEAST I.E., "TRUE GLUCOSE" | LEFT BY YEAST, I.E., "GALACTOSE" | |
|---|---|---|---|---|---|
| | AS GLUCOSE | AS GLUCOSE +GALACTOSE | | AS GLUCOSE | AS GALACTOSE |
| | MG./100 ML. | | | | |
| *Experiment 1* | | | | | |
| Feeding = 75 ml. whole cow's milk (0.2 Gm./kg. galactose) | | | | | |
| Before feeding | 75.5 | 79.9 | 57.8 | 17.7 | 22.1 |
| After 20 min. | 85.5 | 89.9 | 67.8 | 17.7 | 22.1 |
| After 40 min. | 85.5 | 91.7 | 61.7 | 23.8 | 30.0 |
| After 60 min. | 87.5 | 89.0 | 81.0 | 6.5 | 8.0 |
| After 90 min. | 93.2 | 97.6 | 75.5 | 17.7 | 22.1 |
| After 120 min. | 93.2 | 97.6 | 75.5 | 17.7 | 22.1 |
| After 150 min. | 79.5 | 83.9 | 61.8 | 17.7 | 22.1 |
| After 180 min. | 83.5 | 90.9 | 53.4 | 30.1 | 37.5 |
| *Experiment 2* | | | | | |
| Feeding = 120 ml. whole cow's milk (0.3 Gm./kg. galactose) | | | | | |
| Before feeding | 79.9 | 84.5 | 61.4 | 18.5 | 23.1 |
| After 30 min. | 85.5 | 90.4 | 66.8 | 18.7 | 23.6 |
| After 60 min. | 76.9 | 82.8 | 53.5 | 23.4 | 29.3 |
| After 90 min. | 74.0 | 79.1 | 56.0 | 18.5 | 23.1 |
| After 120 min. | 73.0 | 75.8 | 61.8 | 11.2 | 14.0 |
| After 150 min. | 76.0 | 78.8 | 64.8 | 11.2 | 14.0 |
| After 180 min. | 75.5 | 78.3 | 64.3 | 11.2 | 14.0 |
| After 210 min. | 75.5 | 78.3 | 64.3 | 11.2 | 14.0 |
| After 240 min. | 73.0 | 75.8 | 61.8 | 11.2 | 14.0 |
| *Experiment 3* | | | | | |
| Feeding = 100 ml. whole cow's milk + 3 Gm. lactose (0.45 Gm./kg. galactose) | | | | | |
| Before feeding | 77.0 | 79.8 | 65.7 | 11.3 | 14.1 |
| After 1 hr. | 127.0 | 131.9 | 108.4 | 18.6 | 23.5 |
| After 2 hr. | 80.0 | 80.0 | 80.0 | 0.0 | 0.0 |
| After 3 hr. | 77.5 | 77.5 | 77.5 | 0.0 | 0.0 |
| After 4 hr. | 76.0 | 76.0 | 76.5 | 0.0 | 0.0 |
| *Experiment 4* | | | | | |
| Galactose tolerance test, 1.75 Gm./kg. galactose | | | | | |
| Before feeding | 71.0 | 73.7 | 59.8 | 11.2 | 13.9 |
| After 1 hr. | 133.0 | 155.5 | 43.0 | 90.0 | 112.5 |
| After 2 hr. | 117.0 | 130.4 | 63.5 | 53.5 | 66.9 |
| After 3 hr. | 100.0 | 104.7 | 81.3 | 18.7 | 23.4 |

to 41 per cent of the total sugar found in the blood.

From the observations on eight different near-normal infants (Table II), all on regular milk (lactose) feedings, it was again demonstrated that considerable galactose (as much as 40 per cent of the total sugar) may be expected shortly after a feeding, whereas three to four hours later it may have completely disappeared.

The observations in Table III demonstrate that the normal infant not receiving lactose-containing food has no demonstrable galactose in his blood. In the infant with the specific defect in metabolizing galactose, small amounts of galactose could, however, be demonstrated, suggesting the possibility of galactose formation from glucose.

TABLE II. DETERMINATION OF THE RANGE OF GALACTOSE CONCENTRATIONS IN CAPILLARY WHOLE BLOOD AND VENOUS SERUM IN A VARIETY OF NONACUTELY ILL INFANTS RECEIVING REGULAR MILK FEEDINGS

| INFANT | AGE | DIAGNOSIS | TRUE GLUCOSE (MG./100 ML.) | GALACTOSE (MG./100 ML.) | GALACTOSE / TOTAL × 100 |
|---|---|---|---|---|---|
| *Determinations made shortly after feeding* | | | | | |
| Linda W. | 7 mo. | Umbilical hernia | 45.7<br>65.8 | 31.3<br>13.0 | 40.5*<br>16.5 |
| Michael W. | 3 mo. | Cleft palate | 55.3<br>47.8 | 26.0<br>31.9 | 32.0*<br>40.0 |
| Sherman J. | 4 mo. | G. U. anomaly | 55.3 | 26.0 | 32.0* |
| Bonnie F. | 4 mo. | Cleft palate | 34.6 | 26.0 | 37.0 |
| James P. | 2 mo. | Jaundice | 51.2 | 31.0 | 38.2 |
| Lloyd W. | 1½ mo. | Hemangioma | 68.3 | 3.9 | 5.4 |
| *Determinations made about 3 hours after feeding* | | | | | |
| Donald P. | 10 mo. | G. U. anomaly | 63.0 | 0.0 | 0.0 |
| Lena K. | 2 mo. | Cleft palate | 54.9 | 3.9 | 6.6 |

*Determinations on venous serum.

TABLE III. DETERMINATION OF THE RANGE OF GALACTOSE CONCENTRATIONS IN CAPILLARY WHOLE BLOOD IN NONACUTELY ILL INFANTS RECEIVING NO MILK OR LACTOSE-CONTAINING FOOD

| INFANT | AGE | DIAGNOSIS | TRUE GLUCOSE (MG./100 ML.) | GALACTOSE (MG./100 ML.) | GALACTOSE / TOTAL × 100 |
|---|---|---|---|---|---|
| Geoffrey G. | 4 mo. | Allergy (on Nutramigen) | 75.0 | 0.0 | 0.0 |
| Baby R. | Newborn | Diabetic mother | 23.8 | 0.0 | 0.0 |
| Ronald L. | 2½ mo. | Bronchiolitis (on Mull-Soy) | 58.0 | 0.0 | 0.0 |
| Robert T. | 1 mo. | Galactosemia (on Mull-Soy) | 29.2 | 7.8 | 21.0 |
| | | | 59.1 | 3.9 | 6.3 |
| | | | 82.0 | 3.9 | 4.0 |
| | | | 63.7 | 13.5 | 17.5 |

TABLE IV. DETERMINATION OF THE RANGE OF GALACTOSE CONCENTRATIONS IN CAPILLARY WHOLE BLOOD OF INFANTS TREATED FOR DIARRHEA BY STARVATION OR UNDERFEEDING

| INFANT | AGE | TIME | TRUE GLUCOSE (MG./100 ML.) | GALACTOSE (MG./100 ML.) | GALACTOSE / TOTAL × 100 |
|---|---|---|---|---|---|
| James S. | 4 mo. | On admission after I.V. glucose | 230.0 | 37.5 | 16.3 |
| | | After 12 hr. starvation. | 80.0 | 16.3 | 17.0 |
| | | 1st day on D.A.S.* | 106.1 | 3.9 | 3.5 |
| | | 2nd day on D.A.S. | 87.5 | 0.0 | 0.0 |
| | | 3rd day on D.A.S. | 71.5 | 0.0 | 0.0 |
| | | On Alacta + D.A.S. | 59.5 | 13.5 | 18.5 |
| | | On Alacta | 71.0 | 3.9 | 5.2 |
| | | On Alacta | 74.0 | 13.5 | 15.5 |
| | | On Alacta | 71.6 | 3.9 | 5.2 |
| Gwendolyn G. | 4 mo. | On D.A.S. | 37.2 | 0.0 | 0.0 |
| | | On lactic acid milk | 45.7 | 7.8 | 14.6 |
| | | On lactic acid milk | 48.5 | 0.0 | 0.0 |
| | | On lactic acid milk | 63.0 | 7.8 | 10.9 |
| | | On lactic acid milk | 49.6 | 3.9 | 7.3 |
| | | On lactic acid milk | 63.6 | 7.8 | 10.9 |
| | | On lactic acid milk | 37.2 | 0.0 | 0.0 |
| Laritta I. | 2 mo. | On lactic acid milk | 0.0 | 25.0 | 100.0 |
| | 2½ mo. | On lactic acid milk | 54.9 | 7.8 | 12.4 |
| | 3 mo. | On Alacta | 54.9 | 3.9 | 6.6 |
| Gary S. | 4 mo. | On lactic acid milk | 20.0 | 30.0 | 60.0 |
| | | On lactic acid milk | 26.5 | 22.0 | 45.5 |
| Lilly S. | 2 mo. | On D.A.S. | 22.2 | 7.8 | 35.0 |

*Dextrose-Amigen-Salt.

The observations in Table IV demonstrate that infants during periods of diarrhea and underfeeding can develop severe hypoglucemia while still showing normal or even high concentrations of galactose. In some instances the total sugar found would seem to have ruled out hypoglycemia until separation of the two sugars demonstrated marked reduction of glucose.

The data in Table V confirm the findings of others, as reported in the literature,[3-10] that when the clinical picture of "galactosemia" is present, the standard test dose of galactose, 1.75 Gm. per kilogram, leads to much higher and longer sustained blood galactose concentrations than in normal subjects and that true hypoglucemia may develop during the interval of hypergalactosemia.

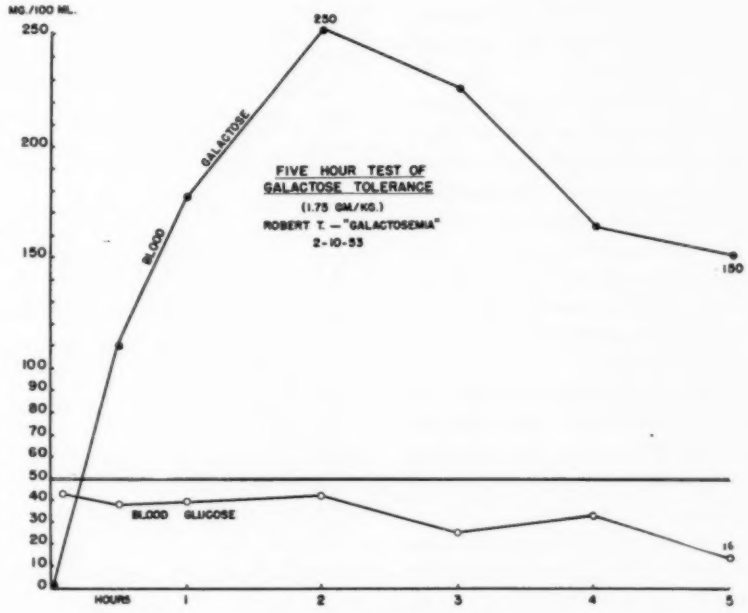


Fig. 4.

TABLE V. GALACTOSE TOLERANCE TEST ON ROBERT T., AGED 3 MO. (GALACTOSEMIA), 1.75 GM./KG. GALACTOSE AFTER EXTENDED NONLACTOSE (MULL-SOY) DIET

| | TOTAL SUGAR | | TRUE GLUCOSE | GALACTOSE | $\frac{\text{GALACTOSE}}{\text{TOTAL}} \times 100$ |
|---|---|---|---|---|---|
| | AS GLUCOSE | AS GLUCOSE + GALACTOSE | | | |
| | MG./100 ML. | | | | |
| Before feeding | 43.0 | --- - | 43.0 | 0.0 | 0.0 |
| After ½ hr. | 126.0 | 148.0 | 38.0 | 110.0 | 74.3 |
| After 1 hr. | 181.0 | 225.5 | 39.0 | 177.5 | 78.8 |
| After 2 hr. | 246.0 | 272.5 | 42.0 | 250.5 | 92.0 |
| After 3 hr. | 208.0 | 253.4 | 27.0 | 226.4 | 89.5 |
| After 4 hr. | 165.0 | 197.9 | 34.0 | 163.9 | 82.7 |
| After 5 hr. | 136.0 | 166.0 | 16.0 | 150.0 | 90.0 |

## SUMMARY AND CONCLUSIONS

In a number of near-normal and sick infants under a variety of circumstances in regard to feedings, determinations were made of the total "true" blood sugar by the Somogyi method of protein precipitation with zinc both before and after fermentation by yeast. In this way glucose and galactose were separated. From such studies it was concluded that:

1. Under ordinary conditions of milk feedings in near-normal infants, as much as 40 per cent of the blood sugar may be galactose.

2. When unusually large amounts of galactose are fed to such infants, e.g., 1.75 Gm. per kilogram, a blood sugar curve very similar to that seen in a normal glucose tolerance test results, with the exception that the rise of sugar is due entirely to galactose. During the early rise of galactose, glucose may fall and then rise later as galactose falls.

3. In essentially normal infants receiving no lactose or galactose-containing food, zero values for galactose and normal values for glucose may be expected.

4. In infants with galactosemia, receiving lactose or galactose feedings, abnormally high values of blood galactose are to be expected, and if galactose and glucose are not separately determined, hypoglucemia may escape detection. The presence of small amounts of galactose in the blood of such infants when not receiving lactose or galactose-containing food suggests formation of galactose from glucose.

5. In infants with diarrhea, when fed milk after a period of starvation or nonmilk feeding, hypoglycemia may also escape detection unless glucose and galactose are individually determined. The frequent high blood galactose values seen in such infants, even while underfed, suggest temporary partial "galactosemia," perhaps the result of illness and milk deprivation.

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# ACUTE POLIOMYELITIS

## A Clinical and Statistical Study of 263 Cases

Emil Smith, M.D., Irwin L. Harris, M.D., and Philip Rosenblatt, M.D.
Brooklyn, N. Y.

IN ANY disease of uncertain course and without specific cure, evaluation of clinical results must be viewed with close objective scrutiny. Poliomyelitis has been known in medical literature for over 110 years[1]; its epidemic character was first enunciated in 1890 by Medin[2] in Sweden. The virus etiology was suggested by Landsteiner and Popper[3] over forty years ago. A multitude of reports cover the intervening period up to the present, and it has become increasingly clear that in recent years figures on mortality and morbidity have generally been in agreement in most sections of the United States despite various regimes of therapy. It is well known that epidemics differ in severity from year to year, even month to month in the same epidemic. The purpose of this paper is to present a clinical analysis of closely observed cases, to point out certain features of bulbar poliomyelitis, and to evaluate the results of therapy.

### METHODS AND MATERIALS

Three hundred thirty-four patients with poliomyelitis were admitted to Kingston Avenue Hospital during the summer and fall of 1950, whereas over 1,000 cases were seen the previous year. This smaller number offered a better opportunity for close clinical observation and more accurate analysis of data than was possible with a larger series. We are reporting on 263 patients in the 1950 epidemic, all of whom were seen by one or more of the authors during the acute phase of the disease. Spinal fluid examinations were done on all cases. Upon termination of the acute phase, all patients were examined by one of two orthopedists on the staff of the hospital, and during the acute phase all diagnoses were confirmed by an attending neurologist. After consultation with the attending orthopedist, patients were either discharged home to the care of their private physician, referred for follow-up in orthopedic clinics, or transferred to orthopedic hospitals for rehabilitation. In accordance with our classification of the disease, nonparalytic and "mild" cases were sent home. Each chart was carefully scrutinized and evaluated as to the accuracy of objective findings. Our plan was to cover the peak months of the epidemic, August, September, and October, including the last week in July since the incidence appeared to rise sharply at that time. The remainder of the 334 patients were seen early in July or late in the fall when the incidence was not at its peak.

### DEFINITION OF TERMS

The nomenclature of the various forms of poliomyelitis remains a con-

From the Communicable Disease Service and Department of Laboratories, Kingston Avenue Hospital, a unit of the Kings County Medical Center.

Read at the Clinical Conference, Kingston Avenue Hospital, March 5, 1953.

fusing subject. This is not surprising when one considers the haphazard nature of the central nervous system involvement, the varying concepts of pathogenesis, the many strains of virus known to produce the disease, and the unpredictability of the outcome.

There is good evidence to show that the manifestations of the disease result from nervous system invasion. Cranial nerve nuclei, the reticulum of the brain, anterior, lateral, and posterior horn cells, as well as the sympathetic ganglia, may all be involved in a given patient, hence a considerable degree of overlap is necessarily present in every classification of this disease. In order to have statistical meaning for comparison we have borne in mind the classifications used by others and have analyzed our cases according to predominance of signs and symptoms. Our classification is modified after Grulee,[4] and is as follows:

I. *Nonparalytic Poliomyelitis:* Patients with evidence of central nervous system involvement without paralysis. Usually with positive spinal fluid findings.

II. *Paralytic Poliomyelitis:*

A. *Spinal Poliomyelitis:* Patients with involvement of the cervical, thoracic, or lumbosacral cord with paresis or paralysis.

B. *Bulbar Poliomyelitis:* Patients with evidence of involvement of cranial nerve nuclei arising from the medulla (bulb)—IX, X, XI, XII, and/or involvement of the vasomotor and respiratory centers. There were thirteen cases involving the medulla and spinal cord (bulbospinal), and these were grouped under the bulbar heading.

C. *Polioencephalitis:* The chief manifestations in this group include involvement of cranial nerve nuclei arising outside the medulla, notably the seventh cranial nerve; also, there are predominant encephalitic symptoms including lethargy, tremors, hallucinations, coma, irrationality, and extreme apprehension.

Spinal poliomyelitis is further subdivided as follows:

I. *Mild:* Includes minimal isolated muscle weakness. All such cases were discharged home to be followed by their private physicians or in orthopedic clinics.

II. *Moderate:* Includes weakness of two limbs.

III. *Moderately Severe:* Includes flaccid paralysis of one limb with or without isolated muscle weakness elsewhere.

IV. *Severe:* Includes flaccid paralysis of two limbs, with or without isolated muscle weakness elsewhere.

V. *Very Severe:* Includes flaccid paralysis of three limbs, or respiratory muscle

TABLE I. AGE RELATED TO SEVERITY OF SPINAL POLIOMYELITIS

| | NO. CASES | AGE 0-6 MO. | AGE 6 MO.-2 YR. | AGE 2-5 YR. | AGE 5-10 YR. | AGE 10-15 YR. | AGE 15-20 YR. | AGE 20-30 YR. | AGE 30-40 YR. | AGE 40-50 YR. | AGE 50+ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total | 263 | 1 | 17 | 60 | 85 | 44 | 25 | 17 | 10 | 3 | 1 |
| Spinal | 132 | 0 | 16 | 35 | 42 | 13 | 14 | 7 | 4 | 1 | 0 |
| Class I Mild | 18 | 0 | 1 | 7 | 5 | 3 | 0 | 1 | 1 | 0 | 0 |
| Class II Moderate | 68 | 0 | 13 | 14 | 21 | 7 | 9 | 3 | 1 | 0 | 0 |
| Class III Moderate, severe | 15 | 0 | 1 | 7 | 6 | 1 | 0 | 0 | 0 | 0 | 0 |
| Class IV Severe | 20 | 0 | 1 | 4 | 6 | 1 | 4 | 2 | 1 | 1 | 0 |
| Class V Very severe | 11 | 0 | 0 | 3 | 4 | 1 | 1 | 1 | 1 | 0 | 0 |

Spinal poliomyelitis is subdivided into five classifications. See text for definitions of this classification.

paralysis (diaphragmatic, intercostals, and abdominals).

The patients in subdivisions II to V upon discharge were sent to orthopedic hospitals for rehabilitation.

INCIDENCE OF FORMS OF POLIOMYELITIS

| | *No. Cases* | *Per Cent* | |
|---|---|---|---|
| Nonparalytic | 71 | 26.9 | |
| Encephalitic | 22 | 8.3 | 22.7 |
| Bulbar | 38 | 14.4 | |
| Spinal | 132 | 50.4 | |

SIGNS AND SYMPTOMS

Fever and lethargy were present in almost all cases, although not noted as such. Constipation was present in most of the patients and was in some cases extremely troublesome. In order of frequency we noted the following common complaints: headache, muscle pain, nausea or vomiting, stiff neck, stiff back, dromedary fever, arterial tenderness, generalized weakness, dysphagia, nasal voice. Uncommon or occasional complaints included hoarseness, aphonia, diplopia, syncope, strabismus, delirium, tremors, nystagmus, dyspnea, and diarrhea.

ONSET AND FEVER RELATED TO SEVERITY OF DISEASE

An attempt was made to correlate the onset of the disease with its subsequent development. It was found that the length or severity of the prodromal stage as evidenced by fever, malaise, headache, or upper respiratory symptoms bore no relation to either the final form taken by the disease or to the severity of paralytic sequelae. In other words, prolonged and severe prodromals could eventuate with mild or nonparalytic poliomyelitis, whereas paralytic poliomyelitis not infrequently appeared without any prodromata.

This fact has been known for a long time. West[5] in 1913 stated that paralytic poliomyelitis was not uncommon in a child who seemingly was well the day before. It was his impression that such children probably had a low-grade temperature not apparent to the parents. In our series, twenty-one, or 16 per cent, of patients with paralytic poliomyelitis had no fever at all, either at time of onset or during the entire hospital stay. In addition there was no direct correlation between fever at time of onset and the type or severity of the disease. In the average case, where present, fever lasted for five to seven days. Prolonged temperature, in our experience, signified disturbance of the heat-regulating center and consequent encephalitic involvement.

SPINAL FLUID

We consider up to 10 cells per cubic millimeter in the spinal fluid a normal finding. In our patients, the cell count ranged on admission from 0 to over 1,000 cells. Over 60 per cent of the cases had a leukocyte count between 10 and 200 with the greatest number in the 50 to 100 cell count range. Occasionally, early in the disease, polymorphonuclear leukocytes predominated. Approximately 5 per cent of our 263 patients had no pleocytosis on admission. This compares with the findings of Nicholls[6] who, in a study of 320 cases over a five-year period, found a normal spinal fluid cell count in 13.8 per cent of her patients.

In the majority of our patients the spinal fluid protein values ranged between 40 and 100 mg. per cent.

We found no correlation between the severity of the disease, or of its form, with either the amount of spinal

fluid protein or with the cell count in the spinal fluid. The outcome likewise bore no relation to these findings. In other words, neither the spinal fluid cell count nor the protein values on admission spinal tap had any prognostic value.

### AGE, SEX, COLOR

Our figures coincide with those of others in that the peak age incidence is in the 5- to 10-year-old group. This group represented about 32 per cent of our cases; the 10- to 15-year-old children represented about 17 per cent.

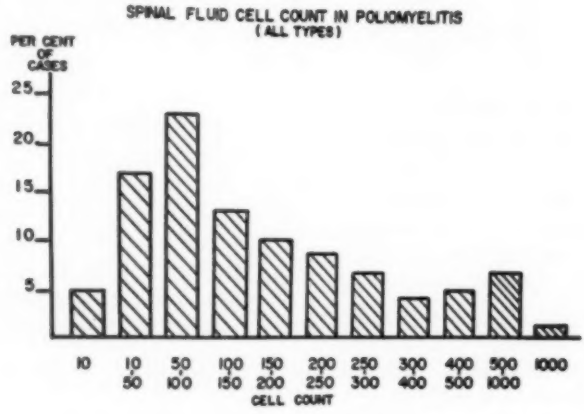


Fig. 1.

TABLE II. SPINAL FLUID CELL COUNTS IN RELATION TO SEVERITY OF POLIOMYELITIS

| CELL COUNT | 10 | 10-50 | 50-100 | 100-150 | 150-200 | 200-250 | 250-300 | 300-400 | 400-500 | 500-1,000 | 1,000 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nonparalytic | | 15 | 20 | 6 | 11 | | 1 | 2 | 2 | 5 | 1 |
| 1. Mild | 2 | 6 | 4 | 2 | 1 | | | 3 | | | |
| 2. Moderate | 7 | 12 | 20 | 10 | 9 | 8 | 4 | 4 | 6 | 6 | |
| 3. Moderate-severe | | 4 | 1 | 2 | 1 | 3 | 1 | | 2 | 2 | |
| 4. Severe | 1 | 2 | 1 | 5 | | 2 | 2 | | 2 | 1 | 1 |
| 5. Very severe | 1 | 3 | | 2 | 2 | | 1 | | 1 | | |
| Bulbar encephalitic | 3 | 3 | 8 | 4 | 1 | 3 | 1 | | | | |
| Deaths | | 1 | 2 | 3 | 2 | 5 | 2 | | 1 | 2 | 1 |

### PERIPHERAL BLOOD COUNT

Leukocyte counts ranged between 5,000 and 16,000 cells per cubic millimeter with the majority of counts under 10,000. The differential count was normal in almost all cases. Where extreme leukocytosis or granulocytosis occurred, a complication was suspected or the presence of a disease other than poliomyelitis.

Our youngest patient in the series was 3 months of age who died of rapidly ascending paralysis, and the oldest patient was a 58-year-old man who died of bulbar involvement.

It has been stated and generally agreed that poliomyelitis is showing an increasing incidence in the older age groups. In Massachusetts, Horton and Rubenstein[7] noted that the peak

age incidence in 1910 was in the 1- to 5-year-old group, but that thirty years later, in 1940, this had shifted to the 5- to 9-year-olds. Dehn,[8] in Cleveland, reported the peak age incidence in the 5- to 9-year-old group, and also that the incidence among those over 15 years of age had more than doubled.

Despite these findings, it is our feeling that the shift of the disease to older age groups is more apparent than real. This opinion is based upon Similarly, 35.3 per cent of the 20- to 30-year-old group and 30 per cent of the 30- to 40-year-old group are nonparalytic in our series. Consequently, it is easy to see how, before spinal puncture became a simple and established procedure, the diagnosis of poliomyelitis would not be made in nonparalytic poliomyelitis, hence eliminating this segment of cases from the over-all totals. Since these nonparalytic cases occur in older age groups,

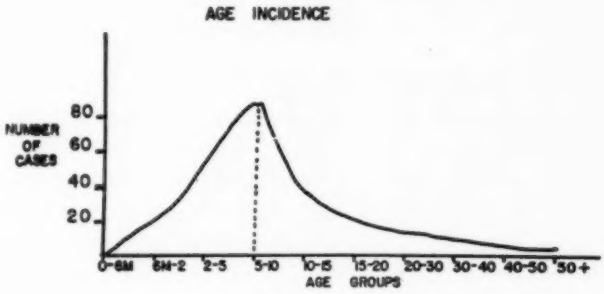


Fig. 2.

TABLE III. CORRELATION OF INCIDENCE OF VARIOUS TYPES OF POLIOMYELITIS TO AGE

| | NO. CASES | AGE 0-6 MO. % | AGE 6 MO.-2 YR. % | AGE 2-5 YR. % | AGE 5-10 YR. % | AGE 10-15 YR. % | AGE 15-20 YR. % | AGE 20-30 YR. % | AGE 30-40 YR. % | AGE 40-50 YR. % | AGE 50+ YR. % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nonparalytic | 71 | 0 | 1.4 | 14.1 | 35.2 | 33.7 | 3 | 8.5 | 4.1 | 0 | 0 |
| Spinal | 132 | 0 | 12.1 | 26.5 | 31.8 | 9.8 | 10.6 | 5.3 | 3.1 | 0.8 | 0 |
| Bulbar | 38 | 2.6 | 0 | 18.4 | 29 | 2.6 | 23.7 | 10.5 | 5.3 | 5.3 | 2.6 |
| Encephalitic | 22 | 0 | 0 | 36.4 | 31.8 | 27.3 | 0 | 0 | 4.5 | 0 | 0 |
| Total | 263 | 0.4 | 6.5 | 22.8 | 32.3 | 16.7 | 9.5 | 6.5 | 3.9 | 1 | 0.4 |

the fact that physicians are much more aware of poliomyelitis today than ever before and diagnosis, especially of the nonparalytic cases, is made more often. It is to be noted (Table IV) that 94 per cent of all cases in the 6-month to 2-year-old group are spinal cases with paralysis or muscle weakness. Diagnosis is relatively easy in this group. On the other hand, 54.5 per cent of all patients in the 10- to 15-year-old group are nonparalytic. Diagnosis in this group is relatively more difficult. the incidence of poliomyelitis in past studies was far lower than it should have been with more accurate diagnostic measures and better physician awareness.

Table III further substantiates the opinion that there is increased recognition of nonparalytic poliomyelitis in the older age groups. Note that 68.9 per cent of the nonparalytic cases fell in the combined 5- to 10- and 10- to 15-year-old groups. It is our considered opinion, therefore, that the age inci-

dence of poliomyelitis has not changed, but that increased awareness of the disease has enabled us to recognize the symptom complex in the older age groups.

The sex incidence in this series coincides with that of others, males being affected predominantly in a ratio of 2:1. Although the disease is considered to be rare in Negroes, 9.5 per cent of our patients were of this race. This compared with a total Negro population in Brooklyn of 7.6 per cent in 1950.[9]

older age groups, the death rate was higher than would be expected according to the case incidence.

These figures suggest that the 10- to 15-year-old patients are better able to tolerate the disease than older age groups. At the same time the prognosis in the older age groups is poor. This impression must, however, remain doubtful since the series of cases is too small to justify definitive conclusions.

### BULBAR POLIOMYELITIS

The highest mortality in poliomyelitis lies in this group. We had thirty-

TABLE IV. COMPARISON OF SPINAL AND NONPARALYTIC POLIOMYELITIS AFFECTING EACH AGE GROUP

| Age | 0-6 MO. | 6 MO.-2 YR. | 2-5 YR. | 5-10 YR. | 10-15 YR. | 15-20 YR. | 20-30 YR. | 30-40 YR. | 40-50 YR. | 50+ YR. |
|---|---|---|---|---|---|---|---|---|---|---|
| Total cases | 1 | 17 | 60 | 85 | 44 | 25 | 17 | 10 | 3 | 1 |
| Spinal | 0 | 16 | 35 | 42 | 13 | 14 | 7 | 4 | 1 | 0 |
| | | 94% | 58.3% | 49.4% | 29.5% | 56% | 41.1% | 40% | 33.3% | |
| Nonparalytic | 0 | 1 | 10 | 25 | 24 | 2 | 6 | 3 | 0 | 0 |
| | | 6% | 16.6% | 29.4% | 54.5% | 8% | 35.3% | 30% | | |

TABLE V. INCIDENCE OF THIRTY-EIGHT CASES OF BULBAR POLIOMYELITIS IN 1950 EPIDEMIC

| Age | 0-6 MO. | 6 MO.-2 YR. | 2-5 YR. | 5-10 YR. | 10-15 YR. | 15-20 YR. | 20-30 YR. | 30-40 YR. | 40-50 YR. | 50+ YR. |
|---|---|---|---|---|---|---|---|---|---|---|
| Deaths | 1 | | | 6 | 1 | 5 | 3 | 2 | 2 | 1 |
| Survivals | | | 7 | 5 | | 4 | 1 | | | |
| Incidence | 2.6% | | 18.4% | 29% | 2.6% | 23.7% | 10.5% | 5.3% | 5.3% | 2.6% |

Encephalitic cases are not included.

TABLE VI. MORTALITY BY MONTH

| | DEATHS | SURVIVALS | TOTAL | % DEATHS |
|---|---|---|---|---|
| August | 12 | 4 | 16 | 75 |
| September | 5 | 9 | 14 | 36 |
| October | 4 | 4 | 8 | 50 |

Total bulbar mortality 55%.
Bulbar and polioencephalitis mortality 35%.

### MORTALITY STATISTICS

Our figures reveal that 29 per cent of all deaths in this series occurred in the 5- to 10-year age group, which is in direct proportion to the incidence of cases in this group (32 per cent). However, the 10- to 15-year age group with a case incidence of 17 per cent accounted for only 5 per cent of deaths in the entire series. In the succeeding

eight true bulbar patients according to our classification, and twenty-two polioencephalitic cases, making a total of sixty falling into this combined group.

It is extremely difficult to compare figures because classifications vary greatly from one clinic to another. As an example, a Minnesota group[10] in 1947 discussed 183 cases of bulbar poli-

omyelitis, breaking them down into five sub groups. The mortality varied from 5 per cent where only cranial nerves were involved to 83 per cent where the circulatory center was affected. The over-all mortality, in this series, was 30 per cent.

Grulee[11] in 1948 reported a 25 per cent mortality in bulbar cases. West and Bower[12] in 1949 reported 129 bulbar cases also with a 30 per cent overall mortality. In our bulbar cases the mortality rate is 55 per cent with exclusion of those showing encephalitic involvement. With the latter included, the mortality rate is 35 per cent, which is essentially similar to the figures cited above.

The survival rate of males to females was 7:1. It appeared that the mortality rate increased with age; the younger the patient the better his chance of surviving bulbar poliomyelitis. Interestingly enough the mortality rate varied with the month. Any kind of treatment would have looked better in September when the mortality was lowest than in August or October, yet treatment was standardized in all cases. Generally when death came it usually struck swiftly, within forty-eight hours after admission of the patient to the hospital. Two of our patients were tracheotomized to no avail. All twenty-two encephalitic cases survived.

## MANAGEMENT OF POLIOMYELITIS

Although it is not the primary purpose of this paper to discuss in detail the therapy of poliomyelitis, the following is a brief résumé of the routines used in the 1950 epidemic at the Kingston Avenue Hospital:

I. *Spinal Poliomyelitis.*—The acute spinal poliomyelitis patients were easy to manage. As soon as they were admitted to the wards they were put to bed on a hard mattress. If they complained of pain or spasm, Priscoline was given every three hours during the day and every four hours during the night, according to a dosage schedule previously described.[13, 14, 15] The standard hospital diet with the usual vitamin supplement was used routinely. Urinary retention was treated by catheterization twice daily or with Furmethide. Constipation was relieved with daily enemas. As soon as these patients became afebrile and free of subjective pain and spasm, they were sent home or to orthopedic hospitals.

II. *Bulbar Poliomyelitis.*—Patients who were unable to swallow, either because of partial or complete palatine or glossopharyngeal paralysis, were treated in the following manner: The patients were put to bed in the prone position upon a hard mattress. They were held in this position by chest jackets, the straps of which were attached to the foot of the beds. The foot ends of the beds were elevated about two feet making an angle of about 30 degrees. If the patients were restless and insisted on turning from side to side, the wrists were padded with cotton and were attached to the sides of the beds. These postures were maintained to assist bronchial drainage.[16] If the mucus was thick and did not drain freely, the mouths of the patients were irrigated and gently suctioned.* Five ounces of a 5 per cent glucose in saline solution at body temperature was introduced by rectum every four hours by means of a funnel and catheter. In addition to the rectal feeding, fluids were given either by hypodermoclysis or by the intravenous route so that a total of 2,000 c.c. of fluid was given daily. Nasal gavage was not begun until the temperature subsided. Regardless of the age of the patient, the amount of feeding given in the first gavage did not exceed 2 ounces, because the patients frequently vomited the first feeding introduced in

*In 1952 Tryptar Aerosol was used to liquefy thick mucoid secretions.

this manner. The amounts were gradually increased until a maximum of 8 ounces every four hours was reached. The gavage feeding consisted of 8 ounces of milk, 2 ounces of sugar, and one egg, plus the standard daily vitamin requirements. Penicillin was used prophylactically and oxygen therapy whenever necessary. Priscoline was introduced slowly, beginning with the afebrile period.

III. *Respiratory Muscle Paralysis.*—The indication for placing a patient in the respirator is a diminution of the vital capacity. The most practical method of recognizing diminished vital capacity is through the use of the counting test.[17] The average patient can count fifty or more during the expiratory phase of the respiratory cycle. Whenever the tonus of the respiratory muscles is lowered, as is the case in poliomyelitis, the vital capacity of the lungs is diminished, and the patient is able to count fewer numbers during the expiratory phase. When the patient is able to reach only the number 3 during the expiratory phase, he is in need of artificial respiration in the respirator. The crucial test as to whether the patient belongs in the respirator is his ability to breathe synchronously with the machine. As soon as the patient is successfully placed in the respirator he becomes a nursing problem under medical supervision.

The average negative pressure maintained in the respirator was 12 to 15 cm. of water.[17] The respiration rate was set at 18 to 22 cycles per minute. The patients were routinely given a high caloric diet with the usual vitamin supplement. Penicillin was administered prophylactically and Priscoline was used routinely for ischemic pain and muscle spasm. Urinary retention was relieved by catheterization or Furmethide.

Improvement in muscle tonus and vital capacity was tested periodically by the counting test. The last number reached was noted, and as muscle tonus improved and the vital capacity increased, the patients were able to count more numbers during the expiratory phase. When the vital capacity reached approximately one-half normal, the patients were asked to cough. When they could cough they were removed from the respirators and observed carefully for cyanosis, excessive perspiration, the use of the accessory muscles of respiration, or somnolence. In the absence of these signs they were sent to convalescent wards. On the other hand, when they were able to breathe without effort, but could not cough, they were kept in the respirators eight out of every twenty-four hours until such time as they regained the ability to cough.

### COMMENTS ON MANAGEMENT

The use of Priscoline in the flushing dose offered relief of pain and spasm in the great majority of cases. When Priscoline was ineffective, hot packs did not bring dramatic relief either. The reason for this is not difficult to understand. Priscoline or hot packs appear to relieve pain by producing vasodilatation and increasing the blood flow to ischemic or relatively ischemic parts. The pain when relieved is an ischemic pain.[18] However, when these measures fail to relieve pain, involvement of sensory nuclei must be present. This pain can only be relieved by measures which block sensory impulses. The sensory fibers terminate in centers within the spinal cord in the cervical and lumbar segments so close to the lateral and anterior motor horn cells that involvement of the latter is almost invariably associated with involvement of the sympathetic or sensory centers.[19] In our series, there were four patients who obtained relief from pain only by the use of codeine.

During the month of August there was little need for Priscoline since

most of the patients did not seriously complain of pain or muscle spasm. In September and October, however, Priscoline was used extensively.

Furmethide was used in selected cases to manage urinary retention with fair results.

Constipation was present in almost all spinal cases and presented a serious problem. Very often manual removal of fecal impactions was necessary.

## DISCUSSION

Tracheotomy presents a controversial matter in the management of bulbar poliomyelitis. Galloway and Seifert[20] reported fifteen consecutive tracheotomized patients over a two and one-half year period with no deaths. These startling figures have not been corroborated by others. Our experience at the Kingston Avenue Hospital has been generally disappointing with this mode of treatment.

If the only difficulty in bulbar poliomyelitis were in the establishment of an airway, tracheotomy would be the method of choice. However, as has been pointed out before, involvement of the respiratory and circulatory centers makes this procedure an empty gesture.

During the summer of 1948 we observed and studied a 14-year-old boy who died in a respirator.[21] His only complaint from the day of admission until he became unconscious and died was "I cannot get my breath." Bronchoscopy showed freely moving vocal cords and no mucous plugs or secretions within the tracheobronchial tree. Pulmonary edema was absent. Nevertheless the patient became cyanotic and suddenly expired.

We concluded that there was a disturbance in the oxygen-carbon dioxide exchange mechanism, that although oxygen was flowing freely, it was not entering the blood stream.

We have postulated peripheral angiospasm to be a common phenomenon in poliomyelitis.[13, 14, 15] We felt that perhaps in this case pulmonary angiospasm acted as a barrier to the exchange of oxygen, leading to cyanosis and death due to acute dilatation of the heart.

During the poliomyelitis epidemic in 1950, history repeated itself. Patients with ascending poliomyelitis and bulbar involvement, or patients with bulbar involvement without laryngotracheal obstruction died the same way as did the poliomyelitis patients in 1949. One morning a patient in a respirator was seen who was cyanotic, unconscious, and foaming from the mouth. It was evident that this patient was dying from acute cardiac dilatation with pulmonary edema. As a measure of desperation, in an attempt to overcome whatever angiospasm existed, we injected 25 mg. of Priscoline intravenously. The cyanosis cleared almost immediately, the mouth foaming stopped, and the patient became conscious and responded to questions. That same afternoon he talked with his wife and we were encouraged to believe that the patient was heading toward recovery. However, late that same afternoon he suddenly became cyanotic and died.

The knowledge gained thus far in dealing with these bulbar cases was that in some there was a barrier that prevented oxygen from reaching the blood and that this barrier could be temporarily set aside by the use of a vasodilator drug.

In 1952 we studied arterial and venous blood pressures in bulbar polio-

myelitis patients. We found that when the vasomotor center was not involved and the blood pressures were normal, postural drainage without tracheotomy generally was sufficient to carry these patients successfully through the acute phase of the disease; other patients showed marked variations in their arterial and venous blood pressures. These pressures rose alternately to unbelievable heights and fell abruptly in a comparatively short time. Such patients if they died did so as a result of acute left or right ventricular failure, secondary to the arterial or venous hypertension. In either case pulmonary edema was a prominent terminal feature. Clinically there were some differences. With arterial hypertension the facies was ashen gray, not unlike that seen in acute coronary thrombosis. With venous hypertension, cyanosis was prominent.

The patients who exhibited arterial or venous hypertension and survived did so because apparently the heart was able to withstand the attack of angiospasm and secondary hypertension. Angiospasm appeared to be released slowly in some cases, abruptly in others. On the other hand, a recurrence of angiospasm could be swiftly fatal. It would seem, therefore, that the bulbar poliomyelitis patients whose tracheobronchial trees are free from obstruction, and whose arterial or venous blood pressures are excessively high, and who have tracheotomies done, recover not as a result of the tracheotomy, but in spite of it. In other words, tracheotomy should be reserved for those bulbar patients who are obstructed. The procedure cannot help the patient whose pulmonary vessels or arteries are in spasm as a result of vasomotor center involvement.

It is our feeling that where there is vasomotor center disturbance, ventilation under a high concentration of oxygen is not sufficient to overcome the alveolar barrier.[22] This barrier is probably pulmonary angiospasm which results in right ventricular failure and pulmonary edema. It is significant to note that in 1934 Landon and Smith,[23] in reporting on the 1931 New York City poliomyelitis epidemic, stated that their fatal cases showed almost invariably a varying degree of right-sided cardiac dilatation. In the more marked cases, left-sided cardiac dilatation was also noted. Some measure of cardiac dilatation was seen in seventy-one of the eighty-one cases studied. It follows, then, that where evidence of cardiac dilatation or failure is present the role of angiospasm in producing this picture should be evaluated. Perhaps the use of vasodilator drugs should be more seriously entertained. Wheatley[24] has recently noted the immediate relief of pulmonary edema in acute left ventricular failure by the intravenous use of Priscoline, similar to that dramatically seen in our patient described above. We have previously postulated the presence of peripheral angiospasm as a cause of muscle pain due to ischemia, and its relief by the use of vasodilator drugs. We have extended our thesis to include pulmonary angiospasm as a result of vasomotor center involvement in bulbar poliomyelitis. Such involvement can in turn induce acute cardiac dilatation which under certain circumstances can be relieved by the use of vasodilator drugs. In any case it gives an explanation for the mechanism of death in those bulbar patients who die regardless of prophylactic or therapeutic tracheotomy.

SUMMARY

Poliomyelitis knows no limitation of age, sex, or race. The term "infantile paralysis" should be discarded in the light of present knowledge. Increased physician awareness of the disease and more frequent recourse to lumbar puncture in suspected cases have contributed to the apparent increase in incidence of the disease as well as to its shift toward older age groups.

We have reported on our experiences in the 1950 epidemic and have reviewed 263 cases studied at the height of the epidemic. More than 25 per cent of our cases were nonparalytic, 22.7 per cent were of the bulbar type, and 50.4 per cent were spinal in type. The over-all mortality rate was 8 per cent. Symptomatology, age and sex ratios, and mortality figures were in general agreement with those reported in other epidemics.

Study of the spinal fluid findings offered no prognostic guide to the extent of paralytic involvement. It assumed only a diagnostic confirmatory role in most instances. About 5 per cent of patients showed no pleocytosis or increased spinal fluid protein values on hospital admission. Similarly the length or severity of prodromal symptoms had no bearing on the ultimate outcome of the disease.

The virulence of the disease varied from month to month and was emphasized. A general plan of treatment of the major types of the disease was given.

The cause of death in poliomyelitis was generally the result of bulbar involvement. The exact mechanism is controversial. We have emphasized the importance of pulmonary angiospasm and have offered this as an explanation for the underlying cause of death. Tracheotomy is of value only when there is tracheobronchial obstruction. This is generally not present in bulbar poliomyelitis. In addition the use of vasodilator drugs, notably Priscoline, has been cited in the treatment of vasospastic phenomena in poliomyelitis.

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# TRANSPLACENTAL TRANSMISSION OF WESTERN EQUINE ENCEPHALOMYELITIS

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AS EARLY as 1892 Ehrlich[1] demonstrated that the semipermeable membrane of the human placenta transmitted antibodies from immune mothers to their infants. Since that time it has been well established that bacterial antitoxins such as tetanus, pertussis, and diphtheria pass from mother to infant via the placenta.[2, 3, 4] Similarly, antibodies to virus diseases such as poliomyelitis and influenza have been shown to traverse the placenta readily.[5, 6] The in utero transmission of immunity to the St. Louis encephalitis virus has been experimentally demonstrated by Smith[7] in mice. Morgan[8] showed similar evidence working with Eastern equine encephalitis virus.

Transplacental transmission of exanthematous infections seems to be thoroughly established. Shuman,[9] in a review of the literature, cites six cases of congenital varicella and adds one of his own. Eight cases of in utero transmission of measles have been reported by Kohn,[10] and Marsden and Greenfield[11] report six cases of mothers who developed smallpox late in pregnancy and who subsequently gave birth to infants who were either born with variola or developed the disease before the eighth day of extrauterine life. Schick,[12] in a complete review of the literature, has gathered some forty cases of infants who manifested lesions of smallpox at birth or too early in life to attribute the illness to contact with the disease. In most of these cases, mothers had been rendered immune to the disease by either vaccination or actual illness some time prior to their pregnancy but during the gestation lived in an area in which smallpox was clinically evident. Although the mothers, themselves, did not suffer a second clinical attack of smallpox, they apparently transmitted the illness to their offspring in utero.

Recently a case of congenital vaccinia has been reported in a 6-month-old premature infant whose mother suffered a severe primary reaction to a vaccination during her third month of pregnancy.[13] The infant was born with extensive skin lesions and died shortly after birth. Intracytoplasmic bodies were demonstrated at autopsy.

Experimentally, the virus of lymphocytic choriomeningitis has been introduced into pregnant mice by Traub,[14] with subsequent demonstration of the virus either in the embryo in utero or in the offspring. Similar experiments with lymphogranuloma venereum virus have been done by Hillendall.[15] Since (a) the particle size

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for Western equine encephalomyelitis (W.E.E.) is smaller than either of the two above viruses mentioned, (b) it is generally accepted that a viremia exists prior to central nervous system invasion with W.E.E.[16, 17] and (c) the rodent and the human being have a hemochorionic type of placenta,[18] it seems logical that this virus should be capable of causing disease in utero in both mice and human beings.

The only report of possible transplacental transmission of arthropod-borne encephalitis in the literature is presented by Mendovy in 1943.[19] Two cases are reported in infants who were seen at the age of 6 and 7 months, respectively, because of gross neurological disturbance. The diagnosis in one instance was based on a positive neutralization test for W.E.E. on the sera of the infant and mother. The second infant and mother had blood taken for complement fixation with a report from the Rockefeller Institute showing "the baby's blood to be positive for Western equine encephalitis in a 1:16 dilution and the mother's positive in a 1:4 dilution." Both infants had a febrile illness within five days of birth but the chronology of illness in the mother is not detailed.

The following are case reports on twins observed in Kern County in the epidemic of W.E.E. in California in 1952.[20]

CASE REPORTS

R. C. and T. C., fraternal twin girls, were born at the Kern General Hospital on Aug. 2, 1952. The infants were delivered by low forceps after a full-term pregnancy and there were no neonatal complications. At birth, T. C. weighed 6 pounds 5 ounces and R. C. 5 pounds 10 ounces. They were in a nursery with ten other infants and taken out for bottle feedings at four-hour intervals. At the age of 4 days, on August 6, the infants were discharged with no apparent abnormality. The mother who was admitted in labor on August 2 was described as preeclamptic with a blood pressure of 180/90. After delivery, she suffered postpartum shock with blood pressure falling to 90/50 and was given 2,000 c.c. of blood. She recovered rapidly, ran an afebrile hospital course, and was discharged with the infants on August 6.

Twenty-four hours after discharge from the hospital, R. C. refused food, ran a temperature of 104° F., and had twitching movements of the extremities. Twelve hours later, the twin, T. C., became ill with a similar clinical picture. They were both readmitted to the hospital the following day, August 9. On physical examination, R. C. was described as a jaundiced, mildly dehydrated, lethargic infant who was acutely ill. Neck was 4+ rigid and the fontanel bulging; temperature was 102° F. Laboratory data revealed a hemoglobin of 14.3; white blood count 18,100 with a shift to the left. Lumbar puncture showed xanthochromic spinal fluid with 695 cells of which 58 per cent were polymorphonuclears. Sugar was 61 mg. per cent, protein was 240 mg. per cent, and culture was negative.

T. C. was described as an acutely ill, dehydrated infant with a "very tense" fontanel. Neck rigidity was 4+ and there was "definite rigidity of extremities." Laboratory data revealed hemoglobin of 16.2; white blood count 22,400 with a shift to left. Lumbar puncture showed xanthochromic fluid with 511 cells of which 76 per cent were polymorphonuclears. Sugar was 68 mg. per cent, protein 238 mg. per cent, with a negative culture.

Admission diagnosis on both patients was probable meningitis, and intensive chemotherapy with penicillin and streptomycin was initiated. The hospital course for both infants was stormy. Temperature ran from 101° to 104° F. for three days. They suffered repeated convulsive episodes.

Oxygen was required for six days, during which time they were extremely lethargic and refused formula. Clinical improvement was noted on the seventh day and they were discharged after thirteen days of hospitalization apparently well but noted to take formula slowly.

Blood specimens during the acute and convalescent phase of the illness were taken for examination for W.E.E. because the infants were admitted to Kern General Hospital at a time when many cases of W.E.E. were being seen and blood for antibody examination was drawn routinely on all patients with a febrile central nervous system disease. Blood drawn on August 11, during the acute phase of illness, showed no significant complement fixing (C.F.) antibodies to be present. This was reported by the Viral and Rickettsial Disease Laboratory, California State Department of Public Health, as a titer of less than 1:8. Blood drawn on August 21 showed T. C. to have a titer of 1:16 and R. C. to have a titer of 1:128. (A fourfold rise in titer is considered evidence of a recent infection. In this case, a rise from $< 1:8$ to 1:16 would have been significant.)

Thus, with this positive evidence for infection with W.E.E. in infants who were only 5 days old and who were out of the hospital less than thirty-six hours prior to the first day of illness, it was felt that further interrogation of the mother was in order.

The following were the significant chronological facts elicited:

(1) On July 21, 1952, the C.'s house was shaken by a rather severe earthquake. Because of this, Mrs. C., who was close to the expected date of delivery, decided to live with her parents in a rural area near Bakersfield.

(2) On July 22, Mrs. C. and her husband slept on the unscreened porch of the parents. They were severely bitten by mosquitoes and decided they would rather return home than spend another night exposed to the mosquitoes. The young mother-to-be had evidence of mosquito bites on her arms and legs.

(3) On July 31, Mrs. C. suffered "feverishness," severe headache, and marked lethargy. She did not seek medical advice.

(4) On August 1, she was taken to Kern County Hospital because of labor pains. It was felt by the examiner that she was not in true labor and was sent home. Although the symptoms of the previous day persisted, she did not relate them to the examining physician because "I was afraid they would keep me in the hospital." The symptoms were less severe than the preceding day.

(5) On August 2, she was admitted to Kern County Hospital in active labor. Because no history of illness was obtained at time of labor, no lumbar puncture or acute blood specimen was obtained from the mother. However, on August 22, or twenty-three days after the onset of the disease, the complement fixing antibodies in the mother's sera were present in a titer of 1:128.

## DISCUSSION

It has been established that the usual transmission of W.E.E. is via mosquito bite and the incubation period is from four to twenty-one days.[21] Since the twins were home less than thirty-six hours prior to the onset of their illness, the disease could only have been contracted either in utero or in the nursery during the first few days of life. It is doubtful that mosquitoes penetrated the nursery but to make this possibility even more remote, the other ten infants in the nursery at the time the twins were there were visited. At the time of the visit, the infants were 5 to 6 weeks old and no history of illness could be elicited. Nine out of ten were bled and C.F. antibody titers in all cases were $< 1:8$. A group of twenty nurses and doctors and other employees who were on the nursery

floor at the onset of illness were also bled and C.F. titers here too were $< 1:8$.

The house of the parents of the young couple was visited and a next door neighbor and forty chickens free in the yard less than 100 yards from the back porch where the couple slept. Twelve of the chickens were bled and 25 per cent of them had a significant titer (an $LD_{50}$ of more than 100) of neutralizing antibodies for W.E.E. In Kern County over the past three years, neutralizing antibodies were present in about 25 per cent of chicken flocks randomly sampled.[22] It has been shown that mosquitoes may transmit W.E.E. experimentally from chicken to chicken,[23] and it is believed that many birds may play an important role as a reservoir host for the W.E.E. virus. The importance of the role of the chicken in the natural transmission of the disease is not clear and indeed it is felt that others of the avian species are probably more important factors.[24] However, they should not be overlooked in the present situation which may be summarized as follows:

A pregnant female was severely bitten by mosquitoes eleven days before term while living in an area where an epidemic of encephalitis in human beings was observed and where infection in chickens (either past or present) has been established. Two days before delivery, the patient had a clinical illness that resembled encephalitis and, subsequently, complement fixing antibodies for W.E.E. were present in the serum. Twin infants were born and on the fifth day of life had clinical and serological evidence of encephalitis. The low initial titers and the subsequent high titers rule out transplacental transmission of antibody and establish a definite etiological diagnosis. The evidence strongly points to transplacental transmission of the virus. Unfortunately, no attempt was made to isolate the viral agent in the acute blood sample.

The infants, seen on Sept. 18, 1952, at 6 weeks of age, were in good health. C.F. titer on T. C. had risen to 1:256 and on R. C. to 1:512. The mother's titer was 1:64.

In conclusion it must be mentioned that just as in the viral exanthematous infections, W.E.E. in the last stages of pregnancy does not consistently produce disease in the offspring. Local factors such as placental defects which may be necessary for in utero transmission of disease are discussed by Goodpasture.[25] In view of the known pathological changes in the placenta associated with pre-eclampsia,[26] the maternal pre-eclamptic state in the present cases may have been an important factor in the in utero infection.

During the present epidemic two other cases of clinical W.E.E. with serological confirmation were observed in pregnant women, the onsets of illness being within one to three days of delivery. The pregnancies were uncomplicated. The infants in both cases were apparently unaffected and did not show any serological evidence of disease either at birth or at 2 months of age.

## SUMMARY

1. Evidence for transplacental transmission of antibodies and viruses is reviewed.

2. Two clinical and serologically proved cases of Western equine encephalomyelitis in twin infants 5 days old

are presented. Evidence strongly suggests transplacental transmission of the virus.

3. Maternal infection with Western equine encephalomyelitis in the late stages of pregnancy does not invariably infect the infant. In utero infection may be dependent upon local placental defects.

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ADDENDUM

The twins were examined again at 7 months of age and development to date appeared normal.

Blood drawn on April 9, 1953 (seven months after illness), demonstrated complement fixing antibodies in a titer of 1:256 in both T. C. and R. C.; Mrs. C.'s titer remained at 1:128.

# WESTERN EQUINE ENCEPHALOMYELITIS

## Clinical Observations in Infants and Children

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DURING the period June, 1952, to September, 1952, throughout Kern County and the San Joaquin Valley, California, an outbreak of Western equine encephalomyelitis occurred. In Kern County there was a total of 124 proved cases of which sixty-six were adults and fifty-eight were children. As diagnosis in this disease is presumptive, the criterion for inclusion in these statistics was a positive complement fixation test showing a rise in titer of two blood specimens taken fourteen days apart. The complement fixation test was done in the Virus and Rickettsial Laboratory of the California Board of Health, Berkeley, Calif.

It became apparent early in the epidemic that children of all ages were being stricken. Consequently all children being admitted to the contagious ward of this hospital that had any history or physical findings suggestive of encephalomyelitis had blood drawn for virology studies. During this period ninety cases were studied: forty-two showed positive studies for Western equine encephalomyelitis, thirty-five showed negative studies for all encephalitides diagnosed by laboratory means, nine showed positive studies for mumps encephalitis, and four showed positive studies for St. Louis encephalitis. Of the thirty-five negative studies, there were ten cases that were considered obvious paralytic poliomyelitis and twenty-five as either nonparalytic poliomyelitis or equine encephalomyelitis with a negative complement fixation test. The ages ranged from 7 days to 12 years.

References to Western equine encephalomyelitis in infants and children are few in number. In 1930 Meyer and associates[1] isolated the virus from the brain tissue of an infected horse in California. Meyer[2] had suspected the occurrence of human encephalitis in 1932. In 1938 Howitt[3] established the relationship of the western equine virus to man. In 1941 Gareau[4] and Fulton[5] reported severe cases in children under 12 years of age. In 1943 Medovy[6] presented a clinical study of seventeen cases occurring in children 1 to 76 weeks in age. Davis[7] reported severe residuals in children in 1940. In 1941 Buss and Howitt[8] and Van Wagenen[9] reported the symptoms and spinal fluid findings of infants proved to be infected with western equine virus. In 1945 Black[10] presented the clinical manifestations of the disease as seen in an epidemic in Colorado. In 1946 Eklund[11] described the clinical findings of a large series of cases in adults and children in Minnesota, and reported a case of respiratory paralysis in a 5-year-old child. In 1947 Boyd[12] described the clinical findings in six infants all of whom recov-

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ered. In all other series fatalities were reported.

It is the purpose of this paper to present a clinical study of forty-two established cases of Western equine encephalomyelitis in the acute phase, and to report briefly five cases with unusual clinical features. A long-term study of the more subtle effects of this disease on the intelligence and neuromuscular balance of these children is now in progress, and is not within the scope of this paper. The study is divided into age groups in order to show the various expressions of the disease in different ages.

## GENERAL CONSIDERATIONS

There were twenty-five males and seventeen females. Three cases were of the Negro race; the rest Caucasian. Patients came from both the rural and urban sections of Kern County. Socio-economic background ranged from the lowest economic group to the upper middle class. Common to all areas was a large number of mosquitoes.

*Group 1, Aged 7 Days to 1 Month* (Table I).—The infants in this group showed no findings typical of the disease. It is noteworthy to mention that only two of the infants had rigidity of all extremities, reported by Medovy to have occurred in all his patients under one year. The predominance of polymorphonuclear cells but a normal spinal sugar served to differentiate this disease from bacterial meningitis. Included in this group of six infants were female twins, 7 days old, and one female 6 days old. Mothers in both cases had positive complement fixation tests for the western equine virus. A paper reporting this disease in twins and proposing transplacental passage of the virus appears in this issue.[13] There were no deaths in this group. Two infants appeared to have severe residuals at the time of examination two weeks after discharge. Average hospital stay was ten days. Duration of the disease from onset of symptoms to disappearance of symptoms was 9.5 days. A brief case report of the 6-day-old female follows:

TABLE I

| Total number of cases | 6 |
|---|---|
| | *Percentage* |
| *Presenting symptoms* | |
| Fever 101° F. or over existing two days prior to admission | 100 |
| Convulsions | |
| None present | 33 |
| Generalized jerking and twitching | 66 |
| Anorexia for two days prior to admission | 66 |
| Drowsiness | 16 |
| Irritability | 33 |
| *Physical findings* | |
| Comatose for one day prior to admission | 16 |
| Fontanel | |
| Normal | 33 |
| Tense | 66 |
| Nuchal rigidity | 33 |
| Rigidity of all extremities | 33 |
| Hyperactive reflexes | 16 |
| *Spinal fluid (total cell count range 242 to 1,362)* | |
| Counts showing predominantly polymorphonuclears | 100 |
| Normal sugar | 100 |
| Elevated protein | 100 |

*Case Report:* D. E., a 6-day-old female, was seen at this hospital because of generalized jerking motions for 12 hours. The child, a full-term infant, was born in another hospital in Bakersfield. Birth history was negative for any unusual trauma or asphyxia. For two days prior to admission, the mother noted that the infant nursed poorly, and was very lethargic. Physical examination revealed an acutely ill infant with jerking motions of the right arm and leg, bulging fontanel, hyperactive deep tendon reflexes, and active Moro reflex. There

was no evidence of infection in ears, throat, and chest. Spinal tap revealed 134 cells with 80 per cent polymorphonuclears, protein 362 mg. per cent, sugar 60 mg. per cent. Blood culture was negative as were tuberculosis and coccidioidomycosis skin tests. Temperature was 102° F. Initial treatment consisted of penicillin and A.S.A. Compound. Temperature was normal in twelve hours and convulsions ceased. Spinal tap on the third hospital day revealed 23 cells, all lymphocytes. On the fifth hospital day, the child nursed well but would not react to light or to noise. The fontanel was normal, but all extremities were extremely spastic. On discharge the eighth hospital day the child appeared to have severe cortical damage. A report from her private physician indicates this child in the past six months has remained very spastic, and is extremely retarded.

On the day of admission blood was also drawn from the mother. Virology studies on the mother's and infant's blood were positive for Western equine encephalomyelitis. A check of the children born at the same time in the same hospital revealed no additional cases. The mother was not ill during the pregnancy. Mosquitoes had been noted in the home, but no old or recent lesions resembling insect bites were seen on the child. In view of the patient's age and the previously known case in twins, this is considered as a probable instance of transplacental passage of the virus.

*Group 2, Aged 5 Weeks to 6 Months* (Table II).—In this group of children there were no fatalities. It is noted that lethargy and drowsiness characterized these children on admission. One child, however, presented no physical findings or history except that of fever. The youngest patients showed a spinal fluid in which the cells were predominantly polymorphonuclears, the oldest a predominance of lymphocytes. The two patients having flaccid paralysis of one arm and leg regained their function two days after admission. Average hospital stay was seven days. Average duration of the disease was 8.3 days. The most severe case was that of a 6-month-old Mexican male.

TABLE II

| Total number of cases | *12* |
|---|---|
| | *Percentage* |
| *Presenting symptoms* | |
| Fever 101° F. or more for two days prior to admission | 75 |
| 101° F. or more for one day prior to admission | 25 |
| Convulsions | |
| None | 16 |
| Generalized twitching and jerking | 33 |
| Involving muscles of one side only | 50 |
| Anorexia for two days prior to admission | 75 |
| Irritability | 25 |
| Drowsiness | 25 |
| *Physical findings* | |
| No physical findings | 8 |
| Alert | 16 |
| Fontanel | |
| Normal | 16 |
| Tense | 83 |
| Flaccid paralysis of one arm and leg | 16 |
| Lethargy and drowsiness | 83 |
| Nuchal rigidity | 16 |
| *Spinal fluid (total cell count range 10 to 1,500)* | |
| Predominance of polymorphonuclear cells | 58 |
| Predominance of lymphocytes | 41 |
| Normal sugar | 100 |
| Elevated protein | 100 |

*Case Report:* D. G., a 6-month-old Mexican male, had sudden onset of fever sixteen hours prior to admission, having been well prior to this time. Birth and developmental history were noncontributory. Two hours prior to admission the child had a severe convulsion involving the left arm and left leg. On physical examination the child was found to have a tense fontanel, convulsive movements of the left arm and leg, flaccid paralysis of the right arm and leg, absent right patellar reflex, and hyperactive left patellar reflex. Temperature was 105.2° F.

Spinal tap revealed 423 cells with 83 per cent polymorphonuclears, normal sugar, and elevated protein. Two hours after admission the temperature was 102° F. and the child was comatose. With a sharp rise in temperature a series of violent left-sided convulsions began. On the second hospital day he remained comatose; all extremities were extremely rigid. The temperature remained between 101 and 103° F. On the third hospital day he was lying in extreme opisthotonos, and the extremities took the position of the so-called decerebrate state. On the fourth day the temperature returned to normal and remained so until the patient was discharged. For the next thirty days he remained extremely spastic, did not recognize nurses or parents, did not react to strong light or to noise, but would respond to pain. Spinal tap on the tenth hospital day was normal. He was discharged on the thirty-sixth hospital day as a severely retarded child on a decerebrate level. Frequent examinations up to three and one-half months after discharge revealed no improvement with the exception that the child responded to parent's voice.

*Group 3, Aged 6 Months to 2 Years* (Table III).—There were no fatalities in this group. Spinal fluid cell counts in this group showed a predominance of lymphocytes in 83 per cent and the cell counts were smaller. The reason for a lymphocytic reaction instead of a polymorphonuclear reaction in the spinal fluid in older children is not known. Included in this group is a case of a 16-month-old white female whose hospital course was characterized by intercostal paralysis. For the other five cases the hospital stay was 6.5 days. Average duration of the disease was 7.8 days.

*Case Report:* L. M., a 16-month-old white female, was apparently well until two days prior to admission. Birth history was normal. The child could walk without support and could say eight to ten simple words. Two days prior to admission she had sudden onset of fever, drowsiness, and vomiting. Drowsiness had become extreme, and the temperature ranged from 102 to 104° F. Physical examination revealed an extremely lethargic child whose neck was rigid, respiration rapid and shallow, and reflexes of lower leg hypoactive. Both lower legs appeared weak. Temperature was 105° F. Spinal count showed 22 cells, all lymphocytes. Five hours after admission the child's breathing was extremely shallow and she appeared semicomatose. Six hours after admission, the child, after drinking several sips of milk, became cyanotic and breathing stopped. In approximately thirty seconds breathing resumed, but almost all intercostal activity was gone as was the gag reflex. She was placed in a mechanical respirator and a tracheotomy was done. Color became pink and remained so. Ten hours after admission her color

TABLE III

| Total number of cases | 6 |
|---|---|
| | *Percentage* |
| *Presenting symptoms* | |
| Fever 101° F. or more for two days prior to admission | 100 |
| Convulsions | |
| None | 16 |
| Generalized twitching and jerking | 50 |
| Involving muscles of one side only | 33 |
| Anorexia two days prior to admission | 100 |
| Drowsiness | 33 |
| Vomiting | 50 |
| *Physical findings* | |
| No physical findings | 16 |
| Alert | 16 |
| Irritability | 100 |
| Nuchal rigidity | 83 |
| Drowsiness | 33 |
| Hypoactive reflexes | 33 |
| Spasticity of one arm | 16 |
| Weakness of one arm and leg | 16 |
| *Spinal fluid (total cell count range 10 to 200)* | |
| Predominance of polymorphonuclear cells | 16 |
| Predominance of lymphocytes | 83 |
| Normal sugar | 100 |
| Normal protein | 100 |

was good, but her arms and legs were continually twitching. Twenty-four hours after admission the feet were in extreme equinus position and the arms and legs rigid. Carbon dioxide combining power was within normal limits. The child remained in respiratory and comatose for six days. In the following six days she became more alert and was left out of the respirator for longer periods as intercostal activity returned. On the thirteenth day a muscle evaluation revealed no weakness or spasticity. The patient was unresponsive to everything but pain. She was discharged on the twenty-fourth hospital day as showing extensive cortical damage but no weakness or spasticity of any muscles. On examination two months after discharge, she vocalized much like an infant 8 to 10 months of age, could walk a few steps, could feed herself, and responded well to all stimuli. Since that time the family has moved from this area and the remarkable recovery could not be followed.

*Group 4, Aged 2 Years to 5 years* (Table IV).—There were no fatalities in this group. Drowsiness, vomiting, and headache characterized this group as distinguished from the younger children. Nuchal rigidity was a major physical finding. Lymphocytes again predominated in the spinal cell count, and normal protein was found in over 50 per cent of the children. With exception of one case reported below, the average hospital stay was 5.5 days; the average duration of the disease was 8.1 days.

TABLE IV

| Total number of cases | *11* |
|---|---|
| | *Percentage* |
| *Presenting symptoms* | |
| Fever 101° F. or more two days prior to admission | 100 |
| Convulsions | |
| None | 90 |
| Involving muscles of one side only | 10 |
| Anorexia one day prior to admission | 28 |
| Irritability | 28 |
| Drowsiness | 81 |
| Vomiting | 72 |
| Headache | 100 |
| Aching thigh muscles | 28 |
| *Physical findings* | |
| No physical findings | 10 |
| Alert | 28 |
| Drowsiness | 72 |
| Nuchal rigidity | 90 |
| Hypoactive tendon reflexes | 45 |
| Spasm of hamstring group | 28 |
| Babinski reflex present | 28 |
| *Spinal fluid (total cell count range 50 to 400)* | |
| Predominance of lymphocytes | 90 |
| Predominance of polymorphonuclear cells | 10 |
| Normal sugar | 100 |
| Normal protein | 53 |
| Elevated protein | 47 |

*Case Report:* H. M., a 3-year-old Mexican male, had sudden onset of fever five days prior to admission. According to the mother, the child was perfectly well prior to onset. Motor, social, and language development were normal. Temperature ranged between 101 and 105° F. Extreme drowsiness was noted for three days. The child had been vomiting all fluids for the last eighteen hours. On physical examination, the patient was observed to be comatose, slightly dehydrated, and to have a temperature of 104° F. The pupils were dilated and did not react to light. The deep tendon reflexes were hypoactive. Spinal tap revealed 36 cells with 75 per cent lymphocytes; sugar 55 mg. per cent; protein 54 mg. per cent. Two hours after admission he had a severe right-sided convulsion; a positive Babinski was noted. On the second hospital day he was comatose, lying in opisthotonos; bilateral ankle clonus and Babinski reflex were noted; constant jerking motions of the right arm and leg necessitated deep sedation. Skull films, nonprotein nitrogen and calcium level were normal. On the sixth hospital day the left arm and leg were flaccid; the head and eyes were deviated to the right; jerking motions were still present on the left side. This continued until the thirteenth day when previous neurological signs dis-

appeared. The child was still comatose; he now moved about with violent thrashing movements of all extremities. He remained comatose until the twentieth hospital day when he appeared to react to light and noise, but the violent thrashing movements continued. On the day of discharge thirty days after admission, the patient ate well, continued to move about violently unless sedation was used, and appeared to be on a decerebrate level. He was discharged to the parents who wanted very much to see what a home environment would accomplish. Two months after discharge, the child was seen in the pediatric clinic; he was well nourished and happy, could talk in simple sentences, could walk, run, and ride a bicycle. Parents stated he ate well and fed himself. No convulsions were noted; he was taking 6 drams of elixir of phenobarbital daily. Further progress will be reported.

*Group 5, Aged 6 to 12 Years* (Table V).—There were no fatalities in this group. These older children showed again a predominance of lymphocytes in the spinal fluid. Headache and vomiting in this age group were persistent and quite severe. One patient showed weakness of both legs on muscle evaluation test plus tenderness on palpation of the large muscle groups, suggesting poliomyelitis rather than encephalomyelitis. Hospital stay, with the exception of one severe case, was 5.5 days. Average duration of the disease was 7.6 days.

*Case Report:* P. Q., an 8-year-old white male, was noted to be quite listless three days prior to admission. Sudden onset of fever 104 to 105° F. was noted for two days. On the afternoon of admission, the fever rose sharply to 104.5° F., and the child had a severe clonic convulsion. Past history revealed a head injury one month prior to illness. The patient was unconscious for five minutes and had a brief clonic convulsion. Skull films and spinal tap at that time were normal. An electroencephalogram was interpreted as showing a lowered convulsive threshold.

Physical examination revealed an extremely restless white male who was well oriented; constant grimacing of face was noted, as well as nuchal and back rigidity. Temperature was 103° F. Spinal tap revealed 112 cells with 94 per cent lymphocytes; sugar 62 mg. per cent; protein 30 mg. per cent. One-half hour after admission the child became comatose. For the next two days coma alternating with irrational periods was observed. Temperature swung between 100° and 105° F. On the third hospital day the head and eyes were turned to the right; weakness of the left arm and left leg was easily demonstrated. Purposeless movements of the right arm and leg were noted when the patient was stimulated by light touch. This picture continued until the sixth hospital day. He became quite rational, responded readily to questions and appeared oriented. A muscle evalution showed weakness of all muscles of the left arm and leg.

TABLE V

| Total number of cases | 7 |
|---|---|
| | *Percentage* |
| *Presenting symptoms* | |
| Fever 101° F. or more for two days prior to admission | 100 |
| Convulsions | |
| None | 86 |
| Generalized jerking movements | 14 |
| Drowsiness | 56 |
| Vomiting | 56 |
| Headache | 100 |
| Irritability | 14 |
| *Physical findings* | |
| Alert | 30 |
| Drowsiness | 70 |
| Nuchal rigidity | 100 |
| Weakness of both legs | 14 |
| Tenderness of leg muscles | 14 |
| Babinski reflex present | 28 |
| Rigidity of back | 56 |
| Kernig reflex present | 56 |
| *Spinal fluid (total cell count range 10 to 2,000)* | |
| Predominance of lymphocytes | 100 |
| Normal sugar | 100 |
| Normal protein | 28 |
| Elevated protein | 74 |

Temperature was normal. Spinal tap revealed 9 cells, 100 per cent lymphocytes; sugar 56 mg. per cent; protein 24 mg. per cent. With physical therapy exercises of the arm and leg the child showed marked improvement in five days. He coordinated very poorly on gross and fine movements, and had an unsteady gait. Seventeen days after admission, the child was discharged; at this time he showed slight facial paralysis, poor coordination, and unsteady gait. Muscle power was normal in all extremities. Reflexes were hyperactive but equal. One month after discharge the child still showed facial weakness and an unsteady gait. Mental powers seemed intact. Two months after discharge left facial weakness was still apparent, gait was steady, coordination was good. An electroencephalogram showed many irritable foci.

### TREATMENT

Treatment was largely symptomatic. Temperature was controlled in all cases except those reported above with A.S.A. Compound in doses of 1 grain per year. In all cases the temperature was normal forty-eight hours after admission except as noted above. Convulsions in the younger age group were controlled with barbiturates, and, in all cases, disappeared when the temperature returned to normal. Only a few patients required parenteral fluids for treatment of dehydration due to vomiting. Penicillin was given in all cases to prevent secondary complications; none occurred. Ascorbic acid in large doses was given in all severe cases and in approximately 40 per cent of the uncomplicated cases. Rationale was provided by a recent paper describing its use in diseases of the central nervous system.[14] Lack of sufficient controls does not permit any evaluation of this drug.

### DIFFERENTIAL DIAGNOSIS

As noted in previous articles,[8, 15] the diagnosis of Western equine encephalomyelitis can only be suspected in an endemic area in the summer months. In the younger age groups showing predominance of polymorphonuclear leukocytes, treatment for bacterial meningitis was begun before the protein and sugar studies of the spinal fluid were complete. A diagnosis of poliomyelitis was made in most cases, showing weakness of arms and legs, and in many cases showing no drowsiness and neurological findings. A comparison between the presenting symptoms and signs of those cases of St. Louis encephalomyelitis and those of Western equine showed no differentiating point. Mumps encephalitis was only suspected by a history of exposure and lack of severe involvement.

### RELATIONSHIP OF LABORATORY TESTS TO SEVERITY

There appeared to be no relationship between the titer of complement fixation tests and the severity of illness. One of the most severe cases had a rather low titer, and many of the mild cases had high titers. The total spinal fluid cell count, the type of cell in the spinal fluid, and the amount of protein did not bear any relationship to severity. Repeated spinal taps on both mild and severe cases showed a reversion to normal in approximately the same length of time. Only a few cases showed elevation of the peripheral white cell count, and these were all very mild cases. None of the severe cases had a hemoglobin or red cell count reduced enough to term the children anemic.

## DISCUSSION

The absence of fatalities in this series may perhaps be attributed to lack of virulence in this epidemic as the majority of the patients presented no real problem in management. The severe cases were four in number and are reported above. The wide variety of symptoms and nurological signs are characteristic of the disease. A changing neurological picture in severe cases is the rule rather than the exception. When one considers the pathology of the disease, a diffuse involvement of the entire brain, a variety of symptoms might be expected. Intercostal paralysis, noted in one case and in several adult cases, indicates that the strain of virus in this epidemic had a much higher affinity for motor centers than that in previous epidemics. The changing spinal fluid picture of gradual shift of predominance of polymorphonuclears in the younger children to a predominance of lymphocytes in the older children is not explained, and may be peculiar to the virus strain involved. Previous papers mention either predominance of lymphocytes or polymorphonuclears in all age groups. The principal symptoms and signs presented by each age group can be found to occur in any of the encephalitides or meningitides if they are studied by age group. It is to be noted, however, that drowsiness is not a universal characteristic of this disease. The apparent recovery of three children with what appeared to be severe residuals has not been reported previously in this disease. Just how much recovery was made will only be determined by long-term study. However, it was an observation in the short-term follow-up that these children recovered much of the lost function. The fact that only two severe residuals were noted in the series may also be due to the strain involved. The concept of transplacental passage of the virus is a new one; this will most likely be supported by more cases in the future.

## SUMMARY AND CONCLUSIONS

Forty-two cases of Western equine encephalomyelitis are reported. The presenting symptoms, signs, and spinal fluid findings are tabulated by age group. Each group had characteristic physical findings and symptoms, but these will not differentiate the disease from any other infection of the central nervous system. Spinal fluid counts in the younger age groups showed a predominance of polymorphonuclears, and in the older age groups a predominance of lymphocytes. Laboratory studies bear no relation to severity and are not useful in predicting the outcome. Rigidity of all extremities previously noted by other observers was noted in only a few cases. The disease can mimic poliomyelitis and bacterial meningitis. Western equine encephalomyelitis should be suspected in all cases showing neurological symptoms in an endemic area in the summer months. Average duration of the disease was 10.6 days; average hospital stay was 8.2 days. Treatment was entirely symptomatic.

Five of the cases with unusual features are presented in detail: one in which the concept of transplacental transmission of the virus is proposed, one showing intercostal paralysis as a complication, one showing a severe residual, and two cases in which marked residual was expected, but in which apparent recovery occurred.

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# THE TREATMENT OF DIPHTHERIA AND DIPHTHERIA CARRIERS WITH TERRAMYCIN

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ANTIBIOTICS have been successfully employed in the treatment of acute diphtheria and of diphtheria carriers. The reports on the use of penicillin are numerous[1, 2, 3, 4, 5] and indicate that with adequate dosage over 75 per cent of patients can be cleared of *C. diphtheriae*. The efficacy of aureomycin,[6] 25 to 50 mg. per kilogram per day, against *C. diphtheriae* was reported from this hospital, and more recently evidence has been published indicating that Chloromycetin[7] and streptomycin are also effective against *C. diphtheriae* in vivo.

In vitro studies show that *C. diphtheriae*[8] is also susceptible to terramycin, polymyxin, bacitracin, and to erythromycin.[9] In this report the effect of terramycin, 50 mg. per kilogram per day, in six cases of acute diphtheria and six diphtheria carriers will be described. All patients acutely sick with diphtheria also received diphtheria antitoxin soon after admission to the hospital. All contact carriers were given terramycin alone. No other antibiotic was employed except as indicated in Table I. Terramycin was given until three negative nose and throat cultures were obtained.

The results are recorded in Table I. Of the six cases of acute faucial diphtheria, one patient had negative nose and throat cultures in three days, four had negative cultures within twenty-four hours, and one patient required seven days to become negative. This represents an average of 2.33 days as compared with an average of 21 days previously reported in patients treated with antitoxin alone at the Willard Parker Hospital, and an average of 5 days in the aureomycin-treated cases at Willard Parker Hospital.

All of the patients with faucial diphtheria had membranes which lasted five to six days. One child had a bull neck and another general adenopathy. Both improved under terramycin treatment. No neurological or cardiac complications were observed although three of the six cases were classified as severely ill. It is not likely that terramycin exerted any specific antitoxic effect since neither penicillin nor aureomycin were antitoxic. No complications due to secondary bacterial or fungus invasion developed during terramycin treatment and the two patients with enlarged cervical nodes improved rapidly while under treatment. All six patients harbored virulent strains of *C. diphtheriae*.

The results in the diphtheria carriers were about the same as those observed in the acute cases. The carrier state was considerably shortened by terramycin. Two patients had negative nose and throat cultures within twenty-four hours, one after two

From the Willard Parker Hospital.

*The terramycin for this study was supplied by the Chas. Pfizer & Co., Inc.

TABLE I. FAUCIAL DIPHTHERIA—TREATMENT WITH TERRAMYCIN

| NAME, AGE, ADMISSION DATE AND NUMBER | CONDITION ON ADMISSION | TERRAMYCIN DOSE DURATION | DURATION (DAYS) POSITIVE CULTURE NOSE AND THROAT | BACTERIAL VIRULENCE V OR NV | LATE COMPLICATIONS |
|---|---|---|---|---|---|
| J. M. 5 yr.<br>7/8/51<br>No. 3927 | Membrane tonsils uvula<br>Very toxic<br>Bull neck | 500 mg. IV q.8h.<br>9/9-9/11<br>125 mg. q.6h.<br>9/12 | 3 | V | 0 |
| H. W. 13 yr.<br>10/25/51<br>No. 4345 | Membrane tonsils pharynx<br>Local edema<br>Toxic | 1 Gm. stat.<br>500 mg. q.6h.<br>10/25-11/13 | 1 | V | 0 |
| B. R. 4 yr.<br>11/25/51<br>No. 4611 | Membrane tonsils<br>Swollen cervical glands | 200 mg. q.6h.<br>11/25-12/1 | 1 | V | 0 |
| P. O'H. 5 yr.<br>11/30/51<br>No. 4661 | Membrane tonsils<br>Gingivitis<br>Stomatitis | 250 mg. q.6h.<br>11/30-12/10 | 1 | V | 0 |
| F. M. 5 yr.<br>12/22/51<br>No. 4974 | Membrane tonsils<br>General adenopathy<br>Spleen large<br>Heterophile negative | 500 mg. stat.<br>250 mg. q.6h.<br>12/22-1/3 | 7 | V | 0 |
| S. A. 5 yr.<br>4/15/52 | Membrane tonsils | 250 mg. q.4h.<br>4/15-4/18<br>Penicillin 600,000 U.<br>1 day before culture became negative | 1 | V | 0 |

TABLE II. DIPHTHERIA CARRIERS—TREATMENT WITH TERRAMYCIN

| NAME, AGE, ADMISSION DATE AND NUMBER | CONDITION ON ADMISSION | TERRAMYCIN DOSE DURATION | DURATION (DAYS) POSITIVE CULTURE NOSE AND THROAT | BACTERIAL VIRULENCE V OR NV | LATE COMPLICATIONS |
|---|---|---|---|---|---|
| C. M. 23 yr.<br>11/25/51<br>No. 4616 | Sore throat | 1 Gm. q.6h.<br>11/25-11/27 | 1 | V | 0 |
| R. O'H. 12 yr.<br>12/18/51<br>No. 4909 | | 500 mg. q.6h.<br>12/19-12/21 | 1 | NV | 0 |
| Z. P. 5½ yr.<br>3/4/52<br>No. 1947 | | 250 mg. q.6h.<br>3/4-3/11 | 4 | NV | 0 |
| Z. R. 5½ yr.<br>3/4/52<br>No. 2650 | Complete nasal obstruction<br>Airway occluded by discharge | 250 mg. q.6h.<br>3/24-4/6 | 3 | V | 0 |
| D. R. 2 yr.<br>5/19/52<br>No. 4174 | | 500 mg. stat.<br>250 mg. q.6h.<br>5/20-5/22 | 2 | V | 0 |
| T. J. 4 yr.<br>5/20/52<br>No. 4179 | | 250 mg. q.6h.<br>5/20-5/31 | 6 | V | 0 |

days, one after three days, one after four days, and one after six days. Of the six carriers only one had a tonsillar exudate. The others were discovered to be carriers under other circumstances. Two of the carriers harbored nonvirulent strains of *C. diphtheriae*. This was learned after terramycin was concluded.

Since the group treated with terramycin was quite small it is difficult to compare the results with those obtained with aureomycin or with penicillin. Nevertheless the impression gained was that for acute faucial diphtheria the results differ very little if at all, whether penicillin, aureomycin, or terramycin is added to the antitoxin therapy. A similar impression is gained from our experience in the treatment of contact carriers of *C. diphtheriae*. The carrier state can be terminated by either penicillin, terramycin, or aureomycin in most patients. Possibly a difference in efficacy of these antibiotics may become evident after larger numbers of patients are treated with terramycin.

## CONCLUSION

Although the number of patients treated with terramycin was small, the results were sufficiently impressive to warrant a report of our observations. These indicated that terramycin like penicillin is effective when given along with antitoxin in the acute cases of diphtheria. Terramycin alone rapidly eliminated *C. diphtheriae* from the nose and throat of contact carriers. Terramycin like aureomycin might be given to patients who are allergic to penicillin, or who harbor bacterial strains resistant to penicillin.

Since we have had very few cases of diphtheria in recent years, it was hoped that by reporting our observations further trial of terramycin would be undertaken elsewhere, and thus a more definitive evaluation of this antibiotic in diphtheria might be forthcoming sooner than if we delayed our report.

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# AGENESIS OF THE LUNG WITH VASCULAR COMPRESSION OF THE TRACHEOBRONCHIAL TREE

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AGENESIS of the lung is often associated with other anomalies but occasionally the absence of one lung may be the only congenital defect of clinical significance. Since an infant who has had a pneumonectomy performed for pulmonary disease may develop normally, one would not expect agenesis of one lung to produce serious symptoms when no other anomalies are present. Yet the literature contains a number of reports of infants with congenital absence of one lung in whom death was attributed to this anomaly alone since no other abnormalities were noted at autopsy. A clue as to a possible cause of death in certain of such patients is suggested by the findings in a case of agenesis of the lung in which a thoracotomy was performed because of progressive respiratory difficulty. The operative findings together with the later postmortem observations indicated the mechanism of the partial intermittent obstruction of the airway which was present in this infant. On the basis of the autopsy findings alone a correct interpretation of the clinical course would probably not have been possible because it was only at operation that the vascular compression of the tracheobronchial tree was evident.

The infant showed only slight respiratory symptoms during the first few weeks of life. Then episodes of cyanosis and respiratory distress of gradually increasing severity occurred. A striking feature of the respiratory difficulty in this infant was the character of the cyanotic episodes. Usually when the infant slept, no respiratory difficulty was noted. There was then no cyanosis or stridor. While awake the infant often appeared to breathe normally and have no cyanosis. Crying, however, resulted in a rapid and alarming change in the infant's condition. Deep cyanosis then occurred. In view of the anatomical findings it is believed that with crying the increased intrathoracic pressure caused compression of the airway by the aorta and an anomalously placed pulmonary artery with resultant interference with ventilation. A complete vascular ring did not surround the trachea and therefore the clinical picture did not simulate that encountered in a double aortic arch. Moreover, the anatomical situation was not amenable to surgical correction.

## CASE REPORT

M. H. was a premature female infant who weighed 3 pounds 7 ounces at birth. She was one of twins but the sibling was macerated. Cyanosis was noted at birth but continuous oxygen therapy was given during the first few days of life and the infant improved. When admitted to Lenox Hill Hospital at 9 days of age the weight was 2 pounds 15 ounces

From the Surgical Service, Lenox Hill Hospital.

and there was no obvious respiratory difficulty. Physical examination of the chest was reported as negative but no x-ray was taken at that time. The infant improved gradually. When 6 weeks of age the respirations became quite rapid and slight retraction of the chest wall was noted on inspiration. At this time on the basis of the physical findings and roentgen examination an incorrect diagnosis of atelectasis of the right lung was made (Fig. 1). During the following weeks the frequency and severity of the respiratory distress increased. Feeding and particularly crying might produce severe cyanosis. Roentgen studies of the esophagus revealed an area of compression without any obstruction (Fig. 2). Bronchoscopy was not done because it was now felt that the child probably had agenesis of the right lung and that the risk of endoscopy in view of the infant's condition was too great to warrant that procedure. It was noted that the child often held her head in an extended position. She tended to become fatigued while feeding. The findings suggested increasing pressure on the trachea which was greatest at times of positive intrathoracic pressure. When 10 weeks of age the child's condition was critical and it was therefore decided to attempt relief of the tracheal compression in spite of the great risk of surgical intervention. The findings at the time of exploratory thoracotomy were as follows:

There was no right pleural space. The heart occupied most of the lower right hemithorax. The pericardium contained a slightly increased amount of clear pericardial fluid. The superior vena cava entered the heart far posteriorly and the aorta arose from the right anterolateral aspect of the heart. The pulmonary artery was not seen. The esophagus, which was dilated, lay posteriorly in the right hemithorax. The aorta appeared approximately of normal size and coursed anteroposteriorly to the left side of the trachea, causing compression and

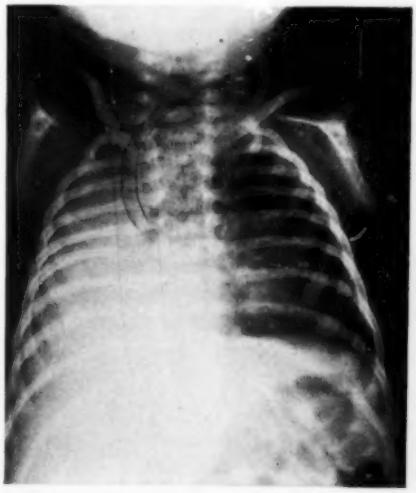


Fig. 1.—Chest roentgenogram taken at 6 weeks of age. Course of the trachea has been outlined. Note the curving of the trachea caused by the aortic arch.

Fig. 2.—Barium-filled esophagus is displaced into the right hemithorax. Note the compression of the upper thoracic portion of the esophagus caused by the aortic arch.

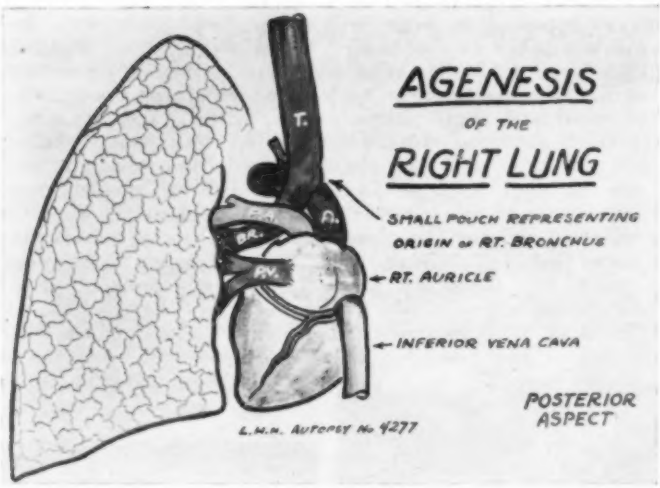
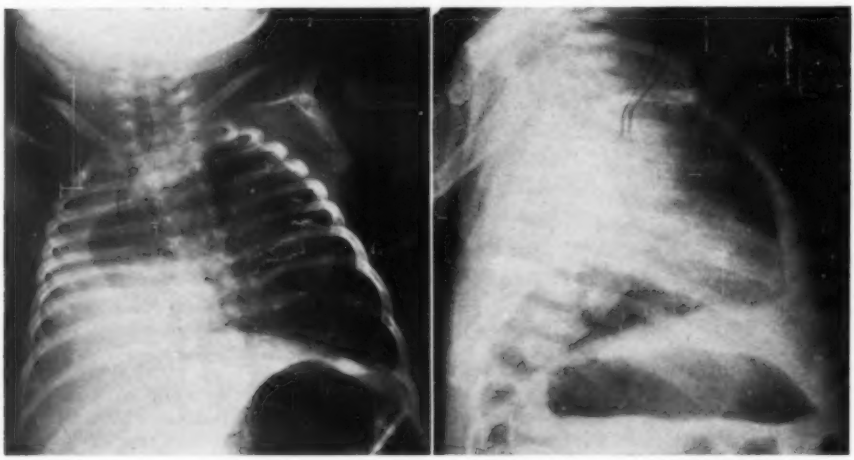



Fig. 3.—Diagram of autopsy findings viewed from posterior aspect. Note that the single pulmonary artery (*P. A.*) to the left lung passes posterior to the bronchus (*Br.*). The aorta (*A.*) passes anterior to the trachea (*T.*) and thus the bronchus is practically encircled by these vascular structures. Only a single pulmonary vein (*P. V.*) was present.



*A* *B*

Fig. 4.—*A*, Chest roentgenogram taken shortly before death. Trachea again outlined. There is now more herniation of the left lung into the right hemithorax. The trachea is quite narrow where it is crossed by the aortic arch. *B*, Lateral roentgenogram of chest shows the trachea (which is outlined) curving backward where it was crossed anteriorly by the aortic arch.

deviation of the trachea. The descending aorta lay more toward the right side than usual. The trachea was thus pushed toward the right and posteriorly by the aorta. An innominate artery arose from the aorta close to the trachea. There was no evidence of any right lung nor was there any evidence of a rudimentary bud from the trachea. The left pleural space extended to the right mid-axillary line. There was no evidence of obstructive emphysema of the left lung. No obvious external abnormality of the heart was detectable. The diaphragm appeared normal. The phrenic nerve overlay the esophagus posteriorly where there was some tissue suggestive of thymus.

At operation it was not found possible satisfactorily to relieve the aortic compression of the trachea. The aorta was freed in the region of the arch. The right phrenic nerve was crushed in order to paralyze the right side of the diaphragm in the hope that this would elevate the heart and perhaps lessen the pull on the aorta. Also several pieces of Gelfoam were packed into the space that had been created surgically in the right hemithorax so as to lessen the mediastinal shift. The infant died the following day.

Post-mortem examination confirmed the operative findings, but at autopsy, because of the lack of distention of vessels, it was not possible to appreciate the aortic compression of the trachea. The right lung was absent and there was only a suggestion of a dimple in the trachea at the site from which a right bronchus should arise. The left lung was pale pink, crepitant, and normally elastic and appeared natural on cut section. A finding of particular interest was that the left pulmonary artery crossed between the trachea and esophagus rather than in its normal position on the anterior aspect of the pulmonary hilum (Fig. 3). As a result of this unusual location of the pulmonary artery the tracheobronchial tree near the root of the left lung was squeezed in between the aorta anteriorly and on the left and by the pulmonary artery posteriorly. The structures did not produce a complete vascular ring around the trachea but did cause angulation and compression of that structure (Fig. 4).

## DISCUSSION

Several reports on agenesis of the lung have analyzed the previously published cases.[1, 2, 4, 5] The recent report of Wexels,[5] to which the reader is referred for a discussion of agenesis of the lung, tabulates the chief features of eighty-seven collected cases and discusses the clinical findings and the radiographic features.

In thirty of the sixty-nine cases in which sufficient data were available there was true aplasia, with no trace of a lung, bronchus, or vascular supply to the affected side. In twenty-eight of sixty-five cases with adequate data no other congenital malformations were recorded, and a considerable percentage of the anomalies present in the other thirty-seven cases were compatible with life. Almost 50 per cent of the patients died in the first five years of life. The cause of death is often difficult or impossible to determine on the basis of the case reports. Most of the cases gave a history of distressed breathing, wheezing respiration, cough, and sometimes of cyanosis, whereas others lived a normal life without symptoms. These data are suggestive that abnormal collapsibility, compression, or angulation of the tracheobronchial tree may be a factor in the high incidence of pulmonary complications in the fatal cases.

Review of the literature did not give us any other information con-

cerning vascular compression of the airway in cases of agenesis of a lung. Unexplained wheezing was reported. In some instances anomalous drainage of some of the pulmonary veins into the right auricle or vena azygos was of significance. More careful radiographic and pathological study of the airway and a search for vascular anomalies of the lung which is present seems indicated in the future. Thomas and Boyden[3] recently reported the first detailed studies of the bronchial and vascular trees in the solitary lung of three cases of agenesis of the right lung. In each instance there were striking deviations in the bronchovascular patterns of the left lung but apparently this lung was normal in size. It is interesting to note that one of these infants who died just after birth had the left pulmonary artery passing posterior to the left bronchus and the tracheobronchial tree was largely encircled by his pulmonary artery and the aorta as in our case.

Although a single lung without obvious fissures is not an uncommon occurrence in cases in which one lung is absent, the studies of Thomas and Boyden suggest that such a lung is usually of normal size and is not merely an overdistended single lobe. Therefore lack of an adequate amount of pulmonary tissue would not seem to be a satisfactory explanation of the relatively high mortality associated with agenesis of the lung.

SUMMARY

A case of agenesis of one lung with respiratory difficulty and death caused by vascular compression of the airway is reported. An anomalous course of the pulmonary artery and the position of the aorta were responsible for the tracheal narrowing. Such vascular compression may not be obvious from post-mortem examinations alone since after death the large arteries are no longer full and tense. Anomalous course of great vessels may be of clinical significance in certain cases of agenesis of the lung which have respiratory difficulty.

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# THROMBOCYTOPENIC PURPURA OCCURRING IN ASSOCIATION WITH PARADIONE (PARAMETHADIONE) AND DILANTIN SODIUM (PHENYTOIN SODIUM) THERAPY

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THE first report dealing with the use of Paradione (3,5-dimethyl-5-ethyloxazolidine-2,4-dione) in the treatment of epilepsy was presented by Davis and Lennox[1] in 1947. Our experience with this drug,[2] based on the treatment of 198 patients who suffered from all types of epilepsy, is in accord with the findings of others.[1, 3-5] We found Paradione to be an effective anticonvulsant for the control of petit mal spells (three per second spike and wave dysrhythmias) but found it considerably less effective than Tridione (3,5,5-trimethyloxazolidine-2,4-dione). Relatively few of our patients who had forms of epilepsy other than petit mal were favorably affected by Paradione therapy.

The only significant untoward reactions of Paradione heretofore observed have been photophobia, cutaneous reactions, and hiccoughs. Eight (4 per cent) of our patients revealed a reduction in leukocyte count and total number of polymorphonuclear cells during the course of Paradione therapy. It is the purpose of this paper to report a case of thrombocytopenic purpura which developed in a child receiving both Paradione and Dilantin Sodium. To our knowledge, no such hematological disturbance has been reported in association with either Paradione or Dilantin Sodium therapy.

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## CASE REPORT

M. M. (H. L. H. A-86983), a 9-year-old white female, was first seen in the seizure clinic of the Harriet Lane Home in August, 1951. Past history revealed that she had had frequent "spells" since the age of 3 years and that she had also suffered with repeated attacks of asthma. There was a history of hay fever on the paternal side of the family.

At the time of this patient's initial visit to our clinic, she was having on the average of two to three minor motor seizures of the akinetic type daily. Her medication for the prior two years consisted of Dilantin, 100 mg. two times a day. She had been previously treated with phenobarbital, Mesantoin, and Tridione without benefit. While taking Tridione, the patient developed "a rash" which disappeared when the drug was discontinued.

Physical examination, including neurological, was within normal limits except for a moderate degree of Dilantin hyperplasia of the gums, enlarged tonsils, and carious teeth. Hemoglobin was 12 Gm. per 100 c.c., and the leukocyte count was 10,400 per cubic millimeter. The differential count was not remarkable except for a 15 per cent eosinophilia. The platelets were reported "normal on smear." Diagnosis of akinetic epilepsy was made and the child was advised to continue with Dilantin, 32 mg. three times a day.

In September, 1951, Paradione, 300 mg. three times a day, was prescribed in addition to the Dilantin. Hemo-

TABLE I

| DATE | GM. HG. | W.B.C. | % POLYPS. | % LYMPHS. | % MONO. | % EOSIN. | % BASO. | PLATELETS | REMARKS |
|---|---|---|---|---|---|---|---|---|---|
| 9- 4-51 | 12 | 10,400 | 37 | 43 | 5 | 15 | | Normal on smear | Initial visit to Harriet Lane Home. Started on Paradione, 300 mg. t.i.d. Continued on Dilantin Sodium, 32 mg. t.i.d. |
| 3-11-52 | 11.2 | 6,050 | | | | | | | Skin rash due to soap |
| 5-17-52 | | | | | | | | | Petechiae, ecchymoses, epistaxis Paradione discontinued |
| 5-19-52 | 12 | 5,200 | | | | | | 80,000 | Neg. tourniquet test 5-28-51 |
| 6- 9-52 | 11.5 | | | | | | | 58,000 | Thrombocytopenia, purpura |
| 6-16-52 | 13 | 7,800 | 57 | 25 | 6 | 12 | | 8,000 | Positive tourniquet test |
| 6-30-52 | 13.4 | 7,300 | 66 | 17 | 7 | 10 | | 4,900 | Purpura persists |
| 7- 2-52 | 13.2 | 13,200 | 74 | 20 | 3 | 2 | 1 | None seen | Purpura persists. Large platelets seen Admitted Harriet Lane Home. Bleeding time 4½ min. Clotting time 8 min. Positive tourniquet test |
| 7- 3-52 | | 7,400 | | | | | | 26,000 | Lupus erythematosus cell prep.-neg. 7/7/52 |
| 7-11-52 | | | | | | | | 9,400 | Bone marrow biopsy Started on ACTH, 50 mg., then 150 mg. cortisone q.d. |
| 7-18-52 | | 7,400 | 66 | 27 | 4 | 3 | | 107,000 | No petechiae or ecchymoses |
| 7-23-52 | | | | | | | | | Bleeding time 4 min. Clotting time 8½ min. Negative tourniquet test |
| 7-25-52 | | 10,500 | 64 | 26 | 9 | 1 | | 244,000 | |
| 7-26-52 | | | | | | | | | Cortisone reduced 100 mg. q.d. |
| 7-29-52 | | | | | | | | 196,000 | Cortisone reduced 50 mg. q.d. |
| 7-31-52 | | | | | | | | | Cortisone discontinued |
| 8- 1-52 | | 7,950 | 41 | 42 | 16 | 1 | | 80,760 | Well |
| 8- 4-52 | | 4,700 | 35 | 44 | 15 | 6 | | 16,700 | |
| 8- 6-52 | | | | | | | | | Well, discharged |
| 8-13-52 | | 6,150 | 48 | 24 | 22 | 5 | 1 | 21,300 | Well |
| 9-15-52 | | 5,150 | 44 | 44 | 9 | 2 | 1 | 73,000 | 9-11-52, 50 mg. cortisone t.i.d. 4 days. Dental extraction |
| 10- 1-52 | | | | | | | | 46,000 | |
| 11- 5-52 | 13.3 | 6,750 | 61 | 25 | 7 | 7 | | 79,000 | Well |
| 12-15-52 | | 6,700 | 52 | 33 | | 14 | 1 | 181,000 | Well. 1/7/53 Dental extraction |
| 1-12-53 | | | | | | | | 29,000 | Bleeding from teeth sockets. Bruises. Prothrombin 50% of normal |
| 1-13-53 | | 6,000 | 40 | 42 | 9 | 7 | 2 | Normal on smear | 200 mg. cortisone, then 150 mg. q.d. |
| 1-16-53 | | | | | | | | 292,000 | 100 mg. q.d. Discharged 1-18-53, well |
| 1-21-53 | | | | | | | | 209,000 | Well |
| 2- 4-53 | | | | | | | | 149,000 | Well |

globin and white cell counts were performed at monthly intervals (see Table I). In March, 1952, she developed an erythematous rash over the hips and groin. This rash disappeared soon after the mother changed the soap she had been using to launder the underclothing.

On May 17, 1952, the mother, who had been cautioned about the toxic symptoms of Paradione, telephoned to state that the child has been bruising easily for two weeks and had had a spontaneous epistaxis. Paradione was immediately discontinued but the Dilantin was continued as before. Positive physical findings were limited to a scattered petechial rash and multiple ecchymotic areas over the lower extremities. There were no oral lesions or lymphadenopathy. The spleen and liver were not palpable. The leukocyte count was 5,200 and platelets totaled 80,000 per cubic millimeter. A tourniquet test was negative. On July 2, 1952, she was admitted to the Harriet Lane Home with a diagnosis of thrombocytopenic purpura, secondary to Paradione therapy. She was afebrile and physical examination was unchanged. The peripheral blood showed a decreased number of platelets and a slight leukocytosis. Bleeding time and clotting time were within normal limits. Tourniquet test was positive. A bone marrow smear obtained by iliac puncture was moderately cellular with some megakaryocytes which did not appear to be producing platelets. There did not seem to be a decrease in the number of megakaryocytes. The proportion of nucleated red cells was decreased and there was a slight increase in the number of eosinophils. A few monocytes were seen. A lupus erythematosus cell preparation was negative. The electroencephalogram revealed abnormalities consistent with a convulsive disorder. On July 11 she was given 50 mg. of adrenocorticotropic hormone by intramuscular injection. The following day cortisone was prescribed, 150 mg. a day by mouth. On the fifteenth day of cortisone therapy, the platelet count had risen to 196,000 per cubic millimeter and all purpuric manifestations had disappeared. The dosage of cortisone was reduced to 100 mg. during the subsequent two days and then to 50 mg. for another two days and then discontinued completely. Approximately twenty-four hours after the cortisone had been discontinued, the platelet count dropped to 80,760 per cubic millimeter and five days later to 16,000 per cubic millimeter. Since there was no recurrence of purpuric manifestations, and she had no seizures while in the hospital, she was discharged on Aug. 6, 1952, to continue with Dilantin, 32 mg. three times a day, and to be followed in the outpatient department.

She had a dental extraction on Sept. 15, 1952, prior to which she was given 50 mg. of cortisone three times a day for four days. In January, 1953, she had three teeth extracted, following which there was a recurrence of petechiae and ecchymoses. She received a third course of cortisone therapy with satisfactory results. At the time of this report (February, 1953), the patient presented no evidence of purpura. The platelet count was 160,000 per cubic millimeter.

## DISCUSSION

In 1950, Everett and Richards[6] reported that hypoplasia of the bone marrow developed in dogs during chronic toxicity studies with Paradione. The occurrence of neutropenia in association with Paradione therapy has been observed in this clinic and reported by others. Dilantin can probably be eliminated as the etiological agent for the following reasons: first, despite its continuous use there has been no progression of the purpuric symptoms, and, second, although Dilantin has been administered to thousands of patients, the occurrence of blood dyscrasias occurring in association with its use is exceedingly rare. Toxic manifestations of Tridione consisting of thrombocyto-

penia, agranulocytosis, and aplastic anemia are well known.[7-11] Since Paradione (dimethylethyloxazolidine) is a homologue of Tridione (trimethyloxazolidine), differing only in the substitution of an ethyl for a methyl group on carbon 5, it is reasonable to assume that Paradione was the toxic factor in this case. This child has an allergic background and had previously been shown to be sensitive to Tridione.

This case points out, once again, the dangers involved in the use of the newer anticonvulsants. The occurrence of toxic disturbances, despite careful laboratory and clinical observations, indicates the importance of instructing the patient or parents to report immediately any untoward reactions which may occur during the course of therapy with any of the anticonvulsant drugs.

SUMMARY

A case of thrombocytopenic purpura occurring in association with Paradione and Dilantin sodium therapy is reported. Paradione appears to have been the etiological agent.

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# THE TREATMENT OF ENTEROBIASIS (OXYURIASIS). THE NEED FOR A SPECIAL SLEEPING GARMENT

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INFESTATION with *Enterobius vermicularis (Oxyuris vermicularis;* pinworm, seatworm, threadworm) is a common disease of children which may also affect adults.

Although the parasites are not highly pathogenic, an almost endless series of conditions have been associated with their presence and with the pruritus ani they produce: insomnia, restlessness, anemia, anorexia, nervousness, enuresis, a lack of sociability, failure in school, picking of the nose, masturbation, toxemia, convulsions, vulvovaginitis, appendicitis, salpingitis, and even peritonitis.

Careful surveys have shown a high incidence in children. Stoll[1] estimated that there are eighteen million cases in the United States and Canada. In Washington, D. C., 35 per cent of preschool children, 51 per cent of school children, and 22 per cent of adults were infested.[2] In New York City, it proved impossible to eradicate the infestation which involved practically all of the children living in a well-conducted orphanage. In one series of appendectomies, 30 per cent of the appendices had worms.[3]

The management of enterobiasis is frequently unsatisfactory. For diagnosis, reliance is often placed upon stool examinations which are virtually worthless. Drugs are used which fail more often than they succeed. Only by understanding the life cycle of the parasite is it possible to approach the problem of treatment rationally.

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## LIFE CYCLE

Infestation with *E. vermicularis* is acquired by the ingestion of the eggs, generally from contaminated fingers. The adult parasites, both male and female, reach maturity and live in the large intestine. They are most numerous in the descending colon, but aggregates are often found in the appendix and in the cecum. The male measures approximately 0.3 x 0.1 cm. and causes little damage. The gravid female, however, is somewhat larger, averaging 1.1 x 0.4 cm. At night, it migrates from the intestinal tract to deposit myriads of eggs in the perianal region. The eggs are embedded in a sticky substance which causes an intense pruritus. The patient scratches the area at night, and then the soiled fingers, with eggs adherent or trapped under the nails, are introduced into the mouth, starting once again the cycle from egg to larva to adult to egg.

The key information necessary to eliminate the infestation is the fact that the adult lives only a few weeks (probably no more than eight weeks) and that if reinfestation does not occur the parasite will be eliminated without medical treatment. Although some authorities[4, 5] claim that eggs deposited in the distal portion of the rectum or in the perianal region may hatch

larvae which return to the large intestine, this must be a rather unusual phenomenon.

The importance of dust-borne infestation has, in our opinion, been exaggerated. If dust were the major factor in transmission then the incidence of enterobiasis probably would be as high in adults and adolescents as in children. While we cannot deny the development of dust-borne infestations, these disappear in the presence of reasonably careful adult anal hygiene.

### DIAGNOSIS

Clinical diagnosis is rarely accurate. Killingsworth and associates[6] stated correctly, "Less than 25 per cent of children with pinworms have symptoms of enough severity to warrant a clinical diagnosis." Definitive diagnosis may be established by observing the adult, generally the female, wandering in the perianal region, or the adult may be visualized in the rectum on proctoscopic examination. Much more frequent diagnosis, however, is made by finding the characteristic eggs which average 55 x 26 $\mu$, are flat on one side, and often contain motile larvae.

Since the eggs are not deposited in the intestinal tract, they will not be found in the stool unless, accidentally, the fecal matter traverses that portion of the perianal tissue in which eggs have been deposited.

The most satisfactory way of making the diagnosis in our experience is a modification of the transparent cellulose (adhesive or Scotch) tape method which was described by Graham[7] and independently shortly thereafter by Jacobs.[8] Watson and MacKeith[9] in a recent article also found this procedure superior. The technique consists of applying a 2 x 6 cm. strip of transparent cellulose tape to the mucocutaneous junction of the anus in the morning before a bath and before defecation. The tape is pressed firmly against the mucous membrane and skin with the back of a test tube or a tongue blade. The strip is then quickly pulled away and the sticky side placed against an ordinary glass slide. The smooth side of the tape is ironed out by gentle pressure to reduce the number of air bubbles. The slide may then be examined directly under the low and high dry powers of the microscope. Cover slips are not needed. With little experience, it is possible to quickly distinguish the ova from the only element which may cause confusion, namely, small air bubbles. Immediate examination is not necessary; the slides may be inserted in an envelope and brought or mailed to a laboratory for diagnosis.

### STANDARD TREATMENT

*Drugs.*—Many drugs have been used but none has been entirely satisfactory. Gentian violet (methylrosaniline chloride) and Diphenan (parabenzylphenylcarbamate) are the best known and probably the most effective. Used alone the cure rate is rarely more than 35 per cent. Other preparations which are employed include hexylresorcinol, tetrachlorethylene, raw garlic or deodorized garlic tablets, Pyribenzamine (tripelennamine hydrochloride), Benadryl (diphenhydramine hydrochloride), Egressin (thymyl N-isoamylcarbamate), bilberries, phenothiazine, bismuth subnitrate, triphenylmethane, santonin, carbon tetrachloride, and aluminum subacetate. Recently terramycin has proved of some

value but its expense and toxicity in the required dosage are considerable, retreatment is often necessary, and the true cure rate has not yet been established. Furthermore, terramycin may simply reduce the number of ova which are released, or merely delay their appearance.

*Accessory Measures.*—Many investigators have recognized that if the cycle of the parasites could be broken specific therapy would be unnecessary or auxiliary. Since the life of the adult female is less than two months, methods which would prevent reinfestation or autoinfestation will be effective in eliminating the parasite. Children have been afflicted with sleeping gloves, their hands have been tied to the sides of the beds, they have been encased in layers of "panties," or pajamas, all with the laudable objective of keeping the fingers from the anus during the sleeping hours. Anyone who has watched children in one of these contraptions will agree that they cannot be successful. Gloves cannot be kept on the hands without strangling the circulation at the wrist. If the hands are tied to the side of the bed and the child cannot bring his fingers to his anus, he generally manages to move in such fashion as to bring his anus to his fingers. And by endless contortions the child generally manages to slip his hand through, under or behind the pants, pajama suit, or other sleeping garment to attain his objective of scratching his itchy anus and incidentally contaminating his fingers with ova. One has only to paint the anal region at night with a dye and examine the child's finger tips in the morning to realize how frequently the anus is scratched at night, even with ordinary safeguards.

Cleansing enemas have been employed with the objective of killing or washing out many of the gravid females. Hexylresorcinol, glycerin, quassia chips, soda and soap have been the favorite medications in this sphere. In addition, various ointments, usually ammoniated mercury and more recently antipruritic and anesthetic preparations, have been applied to the anal region.

And finally, daily vacuuming of rugs, draperies, and furniture, frequent sterilization of the toilet seat, and even household fumigation have at times been employed in an effort to destroy ova—with little success since the ova are more durable than the harassed housewife's morale.

## PROPOSED REGIMEN

Until better drugs are available we must employ the principle that the parasite and its eggs are sturdier than the patient and must be "worn out" by a process of slow attrition. Since the parasites cannot be killed easily or the eggs destroyed simply, it is necessary to reduce the possibility of reinfection while waiting for the short-lived parasite to die. And by reducing the number of eggs available for ingestion the state will be reached when more adults are dying than are growing to maturity in the intestinal tract.

The measures which are advocated are time-consuming and expensive. They may be possible of accomplishment to some families and completely academic to others. But unless the parents are willing to make the necessary sacrifices failure is almost inevitable.

For some years I have experimented with the use of a one-piece sleeping garment which would be effective in preventing patients from scratching the anus during sleep. Several mothers have contributed valuable suggestions and advice.

At present, parents are advised to purchase one-piece pajama suits or BVD's. The buttons are removed and a zipper system is sewn in to seal the smaller transverse rear flap and the longer longitudinal front entrance. These zippers may be "locked" by the use of two safety pins so that the child is sealed in until released by parent. Young children are unable successfully to remove two safety pins. The older children wake up, as a rule, while attempting to remove the pins and if cautioned properly will not scratch the anus. In the few instances where the pins are successfully removed during sleep, it is necessary to substitute ties made of strong string which require cutting for release. We have tried metal locks; if these are large they interfere with sleep; if small, they conceivably could be torn off and swallowed. If there is any objection to the zipper system the rear flap and the lower two-thirds of the front entrance are sewn shut. The upper third of the front entrance may be sealed by ties between closely spaced buttonholes which should be arranged on both sides of the garment.

The pants legs should be narrow so that a hand cannot be slipped up to the anus from below, or pajamas which extend completely over the feet may be purchased. Younger children require the assistance of an adult for the toilet routine and hence this suit offers no additional burden to the parents. Older children capable of a private toilet are prevented from reaching the anus during sleep, but may unseal themselves when awake, without disturbing the parents. After the toilet is completed, the hands, of course, are washed thoroughly. A thin pair of cotton panties should be worn under the pajama suit.

Enough garments must be purchased to permit daily change. Ordinary washing and ironing is adequate. Sheets need not be washed daily. Although the expense involved is not inconsiderable, most parents welcome any method which increases the rate of cure of this persistent infestation.

*Morning Shower.*—An extremely valuable addition to this phase of therapy is a shower with anal washing with soap and warm water in the morning, preferably after defecation, before the child goes to school. A shower in the morning is much more advantageous than a similar washing at night since the eggs deposited during the night are much more numerous than those deposited during the day. The physician will, of course, have to overcome the mother's natural opposition to bathing the child before exposing him to the elements in the morning, but if the objective of changing the customary routine is explained, cooperation is usually obtained. There is, of course, no objection to a shower or a bath at night but usually one such procedure is enough of a burden on the mother. The reason for preferring a shower to a bath must be obvious and is especially applicable when there are several children in the household.

Once emphasis is properly placed upon the primary objective of preventing reinfection, then auxiliary meth-

ods may be employed more realistically.

DRUGS

Since none of the available drugs are very effective, it is our policy to recommend their use in series. This is a safe procedure since the drugs vary considerably in chemical structure and toxicity is not additive.

The following program may be employed:

1. Gentian violet—seven days.
2. Terramycin—three days.
3. Diphenan—ten days.
4. Hexylresorcinol—one day.

worm burden and egg production below the biologic level necessary to perpetuate the infestation. If few eggs are deposited and the adult parasites gradually die off or are killed off, reinfestation will become less and less possible.

After one month's holiday, the entire course of therapy should be repeated if there is any suggestion of persistence of the parasites.

If the patient is unable to tolerate any individual drug it may be eliminated from the regimen. Hexylresorcinol is the most dangerous of these drugs and many physicians may prefer to avoid its use.

TABLE I

| | DRUG | | | |
|---|---|---|---|---|
| | GENTIAN VIOLET | TERRAMYCIN | DIPHENAN | HEXYLRESORCINOL |
| Duration of treatment | 7 days | 3 days | 10 days | One dose |
| Aged 1-2 yr. | 0.009 Gm. (gr. 3/20) b.i.d. | 0.050 Gm. t.i.d. | 0.125 Gm. t.i.d. | Avoid |
| Aged 3-5 yr. | 0.009-0.018 Gm. (gr. 3/20-6/20) t.i.d. | 0.050-0.100 Gm. t.i.d. | 0.25 Gm. t.i.d. | 0.3-0.5 Gm. as one dose |
| Aged 6-10 yr. | 0.018-0.030 Gm. (gr. 6/20-10/20) t.i.d. | 0.10-0.20 Gm. t.i.d. | 0.25 Gm. q.i.d. | 0.6-0.8 Gm. as one dose |
| Aged 11-15 yr. | 0.030-0.060 Gm. (gr. 10/20-20/20) t.i.d. | 0.25 Gm. t.i.d. | 0.5 Gm. t.i.d. | 0.8-1.0 Gm. as one dose |
| Adults | 0.060 Gm. (1.0 gr.) t.i.d. | 0.25 Gm. q.i.d. | 1.0 Gm. t.i.d. | 1.0 Gm. as one dose |
| Time of administration | One hour before meals | After meals | After meals | On fasting stomach in A.M., followed in two hours by saline purge |
| Toxic symptoms | Nausea, headache, vomiting, abdominal pain, diarrhea, dizziness | Nausea, diarrhea, proctitis | Anorexia, diarrhea | Stomatitis if chewed. Epigastric discomfort |
| Contraindications | Ascariasis, hepatic disease, cardiac disease, pregnancy, gastrointestinal disease | | Renal damage | Ulceration of intestinal tract |

The schedule is outlined in detail in Table I.

Until such time as an effective enterobicide is available, the therapeutic accomplishment of drugs may be considered limited to reducing the

*Local Ointment.*—The most efficient local ointment which we have employed is Perazil (chlorcyclizine hydrochloride). This is applied to the anal

region at night with a rubber finger cot—a small amount being tucked into the anal canal. This preparation reduces the pruritus ani and may limit the deposition of eggs.

*Enemas.*—To avoid the bother and traumatic experience of daily enemas, these are reduced to biweekly affairs at night, employing only a small amount of lukewarm water to evacuate those females lurking in the rectum.

*Accessory Measures.*—Clipping of the children's nails, frequent washing of their hands, weekly vacuuming and airing of the house or apartment are simple hygienic procedures which are recommended; they do not inflict an unusual burden upon the housewife.

*Reinfection.*—There is little doubt but that other members of the family, at least the other children, must be treated simultaneously. The greatest difficulty is generally with playmates. If parents attempt to find out from whom the infestation was acquired, their children are often regarded as pariahs and hence there is an inclination to conceal the disease.

The problem is too broad for individual control. Two suggestions may be helpful:

1. Pediatricians and other physicians examining children should routinely employ a Graham cellulose tape test. This will increase the number of diagnoses, "popularize" the disease, and help to remove its social stigma.

2. School physicians should include the test as part of routine annual entrance physical examination.

At present many capable physicians are anxious not to make the diagnosis since they feel frustrated about treatment and see no reason for alarming parents about an unimportant and often "uncurable" disease. This attitude will disappear as soon as therapy becomes more effective and it becomes feasible to treat all cases.

SUMMARY

Since no truly effective enterobicide is currently available, therapeutic efforts should be directed to the prevention of reinfestation by mechanical means and to the reduction of the worm burden and egg production below the biologic level necessary to perpetuate the disease.

These objectives may be attained by:

1. The use of a "seal-in" type of sleeping garment which efficiently prevents anal contamination of the fingers.

2. Morning showers to wash away eggs deposited in the perianal region during the night.

3. Drug therapy which includes several preparations used in any sequence: gentian violet, Diphenan, terramycin, and hexylresoreinol are recommended as reasonably effective and safe.

4. An anal ointment mildly antipruritic and anesthetic. Perazil is suggested.

5. Biweekly enemas employed simply for the purpose of rectal lavage.

6. The usual auxiliary methods of washing hands after the toilet, cleansing the toilet seat once daily, and vacuuming and airing the house once weekly.

7. Simultaneous treatment of siblings and playmates.

8. Greater recognition and popularization of the disease by pediatricians, school physicians, and others so that the social stigma of the parasitization may be removed.

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# THREE UNUSUAL CASES OF MENINGITIS IN CHILDREN

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WITHIN a short period in the summer three unusual cases of meningitis—*Salmonella enteritidis*, typhoid, and pyocyaneus—presented themselves in infants, and were thought worthy of record.

### Case 1. Salmonella Meningitis

A 4-month-old female infant was admitted with a history of fever for four days. The parents, from Iraq, were healthy and had no other children. Pregnancy and birth were normal, and the infant was breast fed for the first month.

Past history was noncontributory, although there were occasional episodes of diarrhea.

Four days before admission, the child developed a high temperature, without cough or diarrhea. Three days later the child started vomiting, and on the day of admission began with generalized twitchings of the body.

On examination, the infant had a temperature of 39.5° C., absent corneal reflex, and convulsions of the whole body, especially of the legs. Neck rigidity was slight, Kernig's sign negative, and tendon reflexes increased on both sides. The liver was palpable, and the spleen was enlarged and firm. On lumbar puncture, the fluid was turbid, under 350 mm. of water pressure, and contained 2,148 cells per cubic millimeter. Protein was 200 mg., Pandy test ++++, sugar 87 mg., chlorides 740 mg. per cent. Urine examination was negative, while the blood count revealed 3,300,000 red cells, and 10,800 leukocytes.

Treatment was begun with penicillin, 400,000 units, and Chloromycetin 1 Gm. daily, and Luminal was given to stop the convulsions. The following day the infant was no better, with convulsions and hyperpyrexia. Kernig's sign was positive, and a right facial palsy was now present.

Culture of the cerebrospinal fluid revealed salmonella, probably *S. enteritidis*, slightly sensitive to streptomycin, and more sensitive to Chloromycetin. Streptomycin ¼ Gm. daily was added to the treatment. After three days, streptomycin was discontinued.

After three days the temperature began to fall; but on the tenth day it rose again to 41° C., spasticity becoming marked, and a slight jaundice apparent. Lumbar puncture revealed 4,508 cells, protein 160, sugar 10 mg., and chlorides 670 mg. per cent. Stool cultures were negative. On the twentieth day the patient became dyspneic, and died with a terminal pneumonia.

A post mortem revealed a diffuse purulent meningitis, with a fibrinous yellowish exudate spread over the frontal gyri, and especially over the base of the brain. Atelectatic foci were present in the lower part of both lungs. Specimens for culture were taken from the liver, gall bladder, spleen, and intestine, and were negative for salmonella. Culture from the cerebrum was positive for *S. enteritidis*, and the type was confirmed by Dr. Kauffmann of The State Serum Institute, Copenhagen.

*Comment.*—Salmonella meningitis is a rather rare condition. The first case was reported by Ghon in 1907, but Netter's review[1] in which he collected seventy-six cases and added two of his own, is the first comprehensive discussion of the subject in the literature. Henderson[2] reported three cases, and

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reviewed 144 cases. Levinson, Kadison and Diamond[3] found that up till 1950 153 cases had been reported.

The genus salmonella contains more than 100 strains of organisms which are pathogenic, and various types have been reported as the cause of meningitis. Beene, Hansen, and Fulton[4] listed eleven types of salmonella which have been isolated in the eighty reports published since 1948, including the typhoid bacillus, and various new types which have been discovered. In their analysis of 235 patients, the condition was four times commoner in children than in adults.

Henderson regards the disease as a septicemia. He maintains that a combination of factors peculiar to the newborn infant makes them especially susceptible, i.e., the high permeability of the intestinal mucosa, with its low resistance to infection, combined with birth trauma leading to a weakening of the meninges. Accordingly, in the newborn infant the condition is epidemic in nature, and characterized by acute diarrhea and a rapidly fatal course. In older children, the sporadic nature, and the frequent absence of diarrhea, makes for a better prognosis. These comments are borne out by Levinson and associates, who found the history of preceding gastroenteritis in at least 80 per cent of the cases. Sources of infection have been contaminated milk (in some cases even mother's milk), water, or food, and can be due to both animal or human carriers.

Although Levinson and co-workers were impressed with the lack of meningeal reaction in their two patients, most observers report the signs and symptoms as that of meningitis in infants, with a high fever and a leukocytosis often present. Cerebrospinal fluid examination is the same as in other purulent meningitides. Diagnosis is difficult and the organism is isolated by a culture of the fluid, or aided by serologic techniques. At autopsy, a purulent meningitis with a tendency to basilar distribution is usually found.

Treatment has varied with time. Henderson[2] regarded sulfadiazine as the probable drug of choice, quoting recovery in ten of nineteen patients, as compared to only eight recoveries in 128 patients not receiving the drug. Penicillin has been regarded as ineffective. Levinson[3] considered streptomycin combined with sulfonamides as the treatment of choice. Cases of recovery have been reported with Chloromycetin[4a] and with intravenous aureomycin.[5]

It remains to be seen whether these new antibiotics will reduce the high mortality in this condition. In Henderson's[2] series, there were 128 deaths in 147 patients, i.e., an 87.5 per cent mortality. Levinson and co-workers[3] feel that the position has improved. Before 1939, eight of 128 patients recovered, i.e., 6 per cent. Since the advent of newer therapy, out of twenty-five patients, twelve recovered, i.e., 48 per cent. Beene and associates[4] found that of eighty-seven cases reported since 1948, seventy-two patients died, giving a mortality rate of 82.7 per cent.

Prognosis generally depends upon the age and type. Henderson reports only one recovery in forty-nine children under one month of age compared to seventeen recoveries in eighty older children. All forty-five patients with infection due to *S. enteritidis* and its varieties died. The use of newer anti-

bioties may, however, lead to an improvement in the prognostic outlook of this condition.

CASE 2. TYPHOID MENINGITIS

A 3-month-old male infant, weight 5 kilograms, was admitted with a history of fever for five days. Family history was noncontributory. Pregnancy and birth were normal, and the child had always been well. Five days previous to admission, a fever developed which did not subside. On the day previous to admission, the child began to have slight difficulty with breathing, and then developed generalized convulsions.

On admission the patient was markedly ill, unconscious, convulsing, with a temperature of 39.8° C. The convulsions were generalized, and included twitchings of the facial muscles. No neck rigidity was present, and tendon reflexes on both sides were hyperreactive. The liver was 2 fingerbreadths palpable, and the spleen 1 fingerbreadth palpable. No evidence of inflammation was present in the ears or throat.

A lumbar puncture revealed a turbid fluid, which contained 1,300 cells per cubic millimeter, and on culture, the etiological organism was found to be *Salmonella typhosa*. Blood and stool cultures were negative, and examination of the urine revealed no significant findings. Examination of the blood showed the absence of any malarial parasite, a hypochromic anemia with 2.5 million red cells, and a white cell count of 8,700, of which 78 per cent were lymphocytes.

On admission the patient was considered as a probable typhoid meningitis, and treatment was instituted with Chloromycetin, 500 mg. daily, in addition to penicillin, 400,000 units, and sulfadiazine, 2 Gm. daily. Luminal was given to stop the convulsions.

The temperature remained high until the fourth day, after which the general condition improved, and sulfadiazine was stopped. From the eighth day onward treatment was continued with Chloromycetin, 250 mg., and penicillin, 200,000 units, daily, until twenty-one days had elapsed. During this period the child was apyrexial and eating well. Diet was normal, with vitamins given in addition. Twelve days after therapy had been discontinued, the child developed a mild diarrhea which responded to a course of sulfadiazine, ½ Gm. daily, and the child was discharged in a healthy condition.

At a follow-up examination two months later, the infant was found to have gained one kilogram in weight, and to be quite well and healthy. The nervous system was normal, and Widal reaction was negative.

*Comment.*—In a comprehensive review, Beene and associates[4] included the typhoid bacillus in their classification of salmonella meningitis. They state, "The typhoid bacillus is now recognized as a member of the genus Salmonella; and its relationship to members of that group is well attested to by its clinical behavior, especially when the meninges are involved." Formerly it was the custom of distinguish clinically between typhoid and salmonella infections. In many cases, however, this can still be done, and the above case is therefore presented under its own heading.

There are very few references in the literature to a true suppurative typhoid meningitis, although meningismus is often to be found in severe cases of typhoid fever. In Mitchell-Nelson's *Textbook of Pediatrics,* typhoid meningitis is regarded as a rare and usually fatal condition. One case is quoted with turbid cerebrospinal fluid, and positive cultures from the spinal fluid, blood, and stools. Death occurred on the eighth day with practically no evidence of intestinal lesion. Petersen[5a] reported a fatal case,

despite cisternal injections of penicillin and sulfathiazole. Höring[5b] reported a case of a 21-day-old infant where the mother was found to be a carrier; and speculates whether infection took place before or during labor, or during breast feeding. A cerebral abscess was found with virulent bacilli in the cerebrospinal fluid. Ripey[6] describes a case of a 13-month-old girl in coma and high fever, which after a number of negative reports turned out to be a typhoid meningitis. Treatment being unsuccessful with penicillin and sulfathiazole, Chloromycetin was used, but with only a slight response, even when increased to 100 mg. every 3 hours. There was a dramatic response, however, when this was augmented with aureomycin, 100 mg. every 3 hours, given orally.

The condition carries a very poor prognosis. Where the disease can be diagnosed clinically, it is therefore advisable to start immediate treatment with large doses of Chloromycetin, augmented, if necessary, by aureomycin.

CASE 3. PYOCYANEUS MENINGITIS (PSEUDOMONAS AERUGINOSA)

A 2-month-old male infant was admitted with convulsions. The parents were from Yemen, and the father was in hospital for tuberculosis. Pregnancy and birth were normal, and the child was always quite well.

Three days before admission the infant had a slight fever, was fretful, did not eat well, and developed a severe diarrhea. Stools were very watery, but did not contain blood. On the day of admission, the child started vomiting and began with generalized convulsions.

On admission, the child was severely ill, dehydrated, with a temperature of 38.5° C., and acidotic breathing. The patient was unconscious and convulsing, especially on the right side of the body. Reflexes were increased on both sides, but no signs of meningeal irritation were present. The stools were watery, but contained no pus or blood.

On lumbar puncture, the cerebrospinal fluid was clear, and not under pressure. Protein and sugar content were normal, but due to a technical error, the cell count and culture of the fluid could not be carried out. The $CO_2$ combining power was 25 vol. per cent, blood calcium 12 mg., and blood urea 180 mg. per cent. Malarial smears were negative, urine normal, and examination of the stools showed the presence of leukocytes and mucus.

The patient was given fluids intravenously including sodium lactate, and Luminal to stop the convulsions. Treatment was also begun with penicillin and sulfadiazine. The following day the patient was worse, with a temperature of 40.5° C., and the heart sounds were rapid, weak, and irregular. The infusion was stopped, and Chloromycetin, 250 mg. daily, was added. Subsequently râles developed at both bases, the patient became dyspneic, and developed a generalized nonpitting edema. Sulfadiazine was stopped, and streptomycin, ½ Gm. daily, begun. The patient's condition worsened, cyanosis developed, and death ensued four days after admission.

At autopsy a severe purulent meningitis was found, with a terminal pneumonia present. Cultures were taken from the cerebrum and the organism was identified as *Bacillus pseudomonas pyocyaneus*, with a moderate sensitivity to streptomycin. Blood agglutinins were negative, but the organism was also present in the spleen, liver, and intestine.

*Comment.*—Although cases of pyocyaneus meningitis have been reported from 1917 onward, the condition is extremely rare, and the organism responsible has been considered a fairly harmless saprophyte. It is now known,

however, that under certain conditions this organism is capable of becoming highly pathogenic, not only by the emission of toxins, but also by direct invasion, causing a severe and often fatal, bacteriemia, both in children and adults.

Most cases have been reported as due to involvement of the meninges secondary to lumbar puncture, head wounds, fracture of the skull, otitis media, etc., or secondary to invasion of the blood stream from a primary focus in the umbilical cord or from an abscess. Several cases have been reported following the intrathecal administration of contaminated material. In a survey of the literature, Kerman and co-workers[8] found twenty cases following lumbar puncture. In eleven cases meningitis complicated diagnostic lumbar punctures, after initial taps had disclosed normal spinal fluid. Seven cases followed spinal anesthetic, and one case was after pneumoencephalography. Since then, Evans,[9] Davidson,[10] and many others have reported usually fatal cases, occurring after spinal analgesia. A few cases have been reported in which the meninges appeared to be the primary involvement.

In a discussion of pyocyaneus in newborn and infants, Zimmerman[11] adds four cases to the ten already recorded in the literature. In these four cases, the presence of an intracranial hemorrhage, probably due to obstetric trauma, and confirmed by autopsy or lumbar puncture, is regarded as a locus minoris resistentiae, leading to an acute purulent meningitis, fulminating in nature and causing death in all four infants. As to the portal of entry, two children had digestive disturbances, and two rhinopharyngitis. The exact pathogenic mechanism could only be conjectured. In the case reported here, the gastrointestinal disturbance may have been the cause of the infection, or, since the fluid was clear, the initial lumbar puncture.

Mortality in this condition has always been high. Evans[9] found the rate to be 66.6 per cent, and that the patients who recovered did so after a long illness lasting from fifty-four to ninety days. Kerman and associates[8] found the gross mortality in fifty-two cases to be 58 per cent. When meningitis was secondary to septicemia, mortality was 85 per cent whereas in primary meningitis mortality was 52 per cent. In a review of ninety cases reported up to 1947, Stanley[15] found the mortality to be 55 per cent in primary meningitis, and 86 per cent in secondary meningitis, with an overall mortality of 68 per cent. Glanzman,[7] however, in discussing the increased virulence of *B. pyocyaneus*, reports recovery in five cases (two of which had meningitis) with the prompt use of antibiotics.

Treatment is varied with time. Wise and Musser (1939) treated six adults with sulfonamides and spinal drainage with four recoveries. Davidson[10] described two adult cases treated with sulfamerazine, of which one recovered. Cairns, and associates[11a] reported three fatal cases, using intrathecal streptomycin and sulfonamides. Debre and Mazzinacci[13] used streptomycin, both intrathecally and intramuscularly, on three infants, with recovery in one. Glanzman[7] reported recoveries in two cases of meningitis, treated with penicillin, sulfadiazine, and streptomycin. Radke and Cunningham[14] reported a child with a double infection, both *B. pyocyaneus*

and *N. flavescens,* who made a prompt recovery on penicillin and streptomycin (intrathecally and intramuscularly). Zimmerman,[11] discussing four cases in newborn infants, found that combined treatment with penicillin, sulfonamides, and streptomycin produced a temporary recovery, with clearing of the cerebrospinal fluid, only to be followed by an acute exacerbation, resulting in the death of all four patients. Aureomycin, given orally, rectally, and intravenously, has resulted in the recovery of a case, as reported by Netter.[16a] Recently, Knight, Hardy, and Negrin[17] reported a case treated successfully with intrathecal streptokinase and streptodornase, together with treatment with neomycin. Yow[16] reported that in fifty-six cases of pyocyaneus infection, the most effective agent in treatment was polymyxin B, with an occasional response to streptomycin and terramycin. It is to be hoped that the use of the newer antibiotics may result in more recoveries in the future.

## DISCUSSION

The occurrence of these three cases within a short period, and the growing number of cases reported in the literature, suggest that these forms are common enough to warrant consideration in any case of meningitis. It may be that cases of this nature are on the increase due to the effectiveness of antibiotics in eliminating the more sensitive organisms as the etiological agent. Yow, in a study of pyocyaneus and proteus infections, maintains that the suppression of other bacteria by widespread use of antimicrobial drugs has increased the relative importance of these organisms as causative agents in infectious processes. Cases of infection due to these organisms, that develop during or following repeated courses of antibiotic therapy, are reported. It seems likely that the same may hold for infections by salmonella or typhoid organisms.

These types of meningitis for various reasons are far commoner in children than in adults, especially in debilitated or dystrophic infants. In many instances, the portal of entry has been regarded as the gastrointestinal tract. The occurrence of these three cases during the summer period in Israel, where over 85 per cent admissions to the unit were cases of gastrointestinal disturbance, emphasizes the necessity of being aware of these conditions, and treating accordingly.

In all cases of convulsions, therefore, a lumbar puncture should be done, and a culture and sensitivity test for organisms carried out, in order that prompt and effective antibiotic therapy can be instituted.

## SUMMARY

Three unusual cases of meningitis —*S. enteritidis,* typhoid, and pyocyaneus—presented themselves within a period of seven weeks in the pediatric department. All three patients were in a serious condition, and had convulsions on admission. Two died and one recovered. The incidence, mortality, and treatment in each type are discussed. It is suggested that these unusual forms may be on the increase due to effective elimination of the more sensitive organisms by antibiotics. Lumbar puncture, culture, and sensitivity test for organisms are advised in any child presenting with convulsions.

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# ACUTE (INFANTILE) GAUCHER'S DISEASE

## Report of a Case, the Second in a Family

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In 1882 Gaucher[1] described the disease that bears his name. In 1927 Oberling and Woringer[2] pointed out that the disease in infancy, in contrast to its chronicity in later childhood and adult life, was distinguished by an acute malignant course, early death, striking tendency to neurological symptoms, and lack of pigment disorders. Summaries of the literature of Gaucher's disease in infancy and childhood have been made by Atkinson[3] in 1938, by Aballi and Kato[4] in 1938, and by Stransky and Davis-Lawas[5] in 1949. Of the approximately thirty reported cases in infants only four have been from the North American continent. The object of this paper is to report an additional case and to comment on the familial occurrence of the disease.

### CASE REPORT

The patient was first seen by one of us (A. K. G.) at the age of 3½ months and admitted to hospital where the diagnosis of Gaucher's disease was confirmed by examination of splenic puncture fluid, by postmortem histology, and by lipid analyses of the spleen and liver.

The parents, aged 36 and 33 years, were healthy, of English and Dutch non-Semitic origin, with no known history of disordered lipid metabolism in antecedent generations. Sternal marrow showed no cells identifiable as Gaucher's in either parent. There were three pregnancies. The product of the first was a girl who died in the Hospital for Sick Children, Toronto, in 1950 at the age of 11 months of Gaucher's disease and was the subject of a report by Rodgers and Jackson.[6] The second child, a boy, when examined at the age of 3 months, showed a spleen palpable 1 cm. and a liver 1.5 cm. below the costal margin. At the age of 2 years neither liver nor spleen was palpable, the child was robust, and sternal marrow was negative for Gaucher cells.

The third child, a male, was first seen at the age of 3½ months because of a collection of mucus in the throat with noisy breathing and difficulty in swallowing. These symptoms dated from the age of 2½ months and were identical to the initial symptoms appearing at the age of 3½ months in the sister who had died of Gaucher's disease. The birth history was normal and there were no previous illnesses except a mild coryza. Examination showed a poorly nourished pale child with circumoral grayness, noisy breathing, rasping cry, much mucus in the pharynx, spleen enlarged into the pelvis, liver edge 3 cm. below the costal margin, and enlargement of all the superficial lymph glands. There were no areas of skin pigmentation and no changes in the conjunctivae. Additional examination in hospital gave the following results: red blood cells 3,530,000, hemoglobin 9.4 Gm., white blood cells 8,900, differential count not unusual, fragility and sedimentation rate of red cells normal. Platelets, coagula-

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tion time, and clot retraction were normal, and prothrombin time 24 sec. Spinal fluid examination including culture was negative. The fundi were normal. Irregular fever to 103° F. was present throughout the hospital stay with nothing other than his disease to explain it. Head retraction, opisthotonus, and hypertonicity appeared and together with the dysphagia and laryngeal difficulty steadily increased. Sternal marrow showed no cells identifiable as Gaucher's. Splenic pulp obtained by puncture showed many large cells of the reticulum cell type, with large granular eccentric nuclei and an abundance of cytoplasm without a binding cell wall. The protoplasm was arranged in fine fingerlike strands and was much paler-staining than the nuclei.

Repeated examination both early and late in the course of the disease failed to show similar cells in the saliva which accumulated in the pharynx. Urinalysis was negative and blood sugar normal. X-rays of the thorax and of the dorsal and lumbar spine showed no abnormalities. Chemical analyses of the blood showed total fats 910 mg. per cent (normal 500 to 800), fatty acids 725 mg. per cent (normal 300 to 400), total cholesterol 123 mg. per cent (normal 150 to 250), cholesterol esters 85 mg. per cent.

After ten days in hospital the child was discharged to his home where the cachexia, opisthotonus, and dysphagia increased, and he died at the age of 10 months after seven and one-half months of illness.

*Pathology.*—At post-mortem examination the body was that of a poorly nourished, poorly developed male infant. The length was 59 centimeters, and the weight was 3,700 grams. The skin and conjunctivae were pale and not pigmented. No teeth were present. The spleen weighed 170 grams, sixteen times the normal of 11.5 grams,[7] and filled most of the left half of the abdomen. It was gray-red and its capsule was coarsely granular.

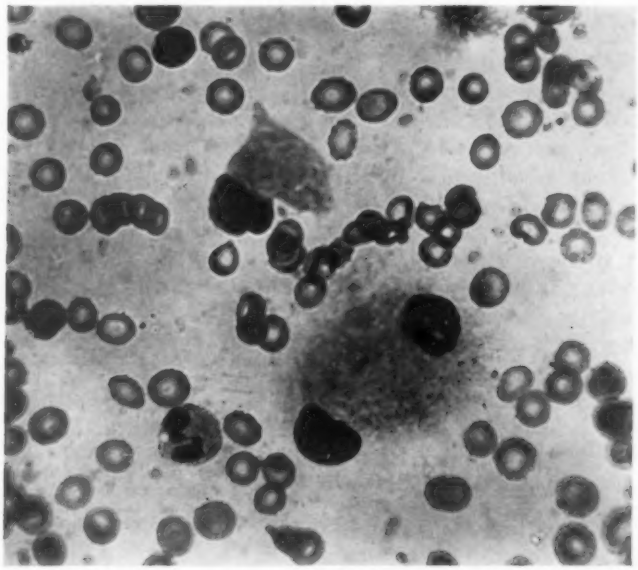

Fig. 1.—Splenic pulp, obtained by puncture of spleen, showing two Gaucher cells. (×900.)

The cut surface was gray. There were several accessory spleens, the largest measuring 1.5 cm. in diameter. The liver weighed 270 grams (normal 160 grams) and filled the upper third of the abdominal cavity. It was gray-yellow both on the external and on the cut surface. The mesenteric lymph nodes and the peribronchial and mediastinal nodes were slightly more prominent than usual and were soft and somewhat gelatinous on the cut surface. The marrow of the vertebrae and long bones was uniformly pale red. The right lung weighed 75 grams and the left 65 grams (normal 61 grams each). The lungs were slightly hyperemic and edematous and showed no consolidation. The cut surface was faintly mottled with white. Other organs showed no abnormality.

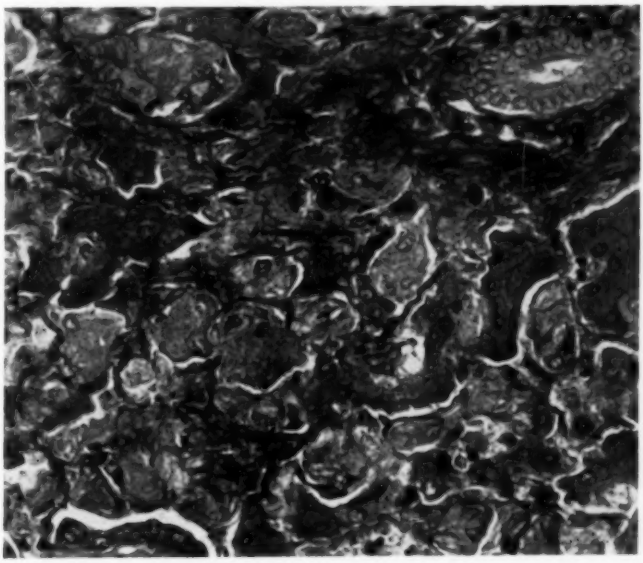

Fig. 2.—Liver, showing compression of liver cords by Gaucher cells—large polygonal cells with several eccentric, frequently vesicular nuclei, and pale, fibrillar cytoplasm looking like wrinkled tissue paper. (×450.)

Typical Gaucher cells were found microscopically in large numbers in the spleen and accessory spleens, liver, lymph nodes, bone marrow, thymus, and lungs. Fewer were seen in the adrenals and in the lymphoid follicles of the intestine. The cells were large and polygonal and had pale acidophilic fibrillar cytoplasm. They usually had several eccentrically placed nuclei varying greatly in size, shape, and staining properties and frequently showing several nucleoli. The cytoplasm had the fibrillar appearance like wrinkled tissue paper typical of these cells. It was particularly well seen on the Mallory-Heidenhain technique, in which the cytoplasm stains gray-blue and the nuclei red. Periodic acid-Schiff stains showed a positive reaction only in patches and was considered inconclusive as a differentiation between Gaucher cells and Niemann-Pick cells.[8, 9]

The lungs contained many Gaucher cells in the alveolar septa, the alveolar spaces, and the bronchial lumina. There were slight hyperemia and edema of both lungs, with here and there scanty infiltrations of polymorphonuclear leukocytes, plasma cells,

and lymphocytes into the edema fluid. The architecture of the splenic and thymic tissue was almost obliterated by a diffuse infiltration of Gaucher cells. The liver was affected to a lesser extent.

The brain was not remarkable externally. Sections taken at random showed the large- and medium-sized pyramidal cells of the cerebral cortex to have a densified appearance, the Nissl bodies being huddled together so as partly to obscure the nucleus—the appearance described as mummification. In addition, their contours were concave and retracted. No vacuoles were seen in the neurons.

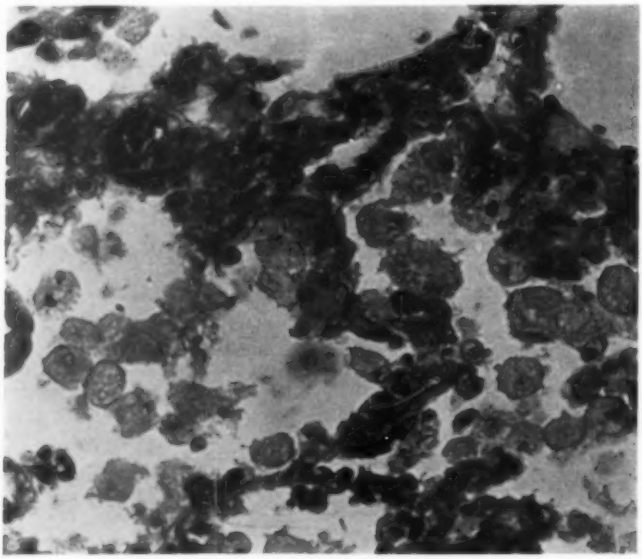

Fig. 3.—Lung, showing Gaucher cells in the alveolar spaces and alveolar septa.

The anatomical diagnosis was Gaucher's disease.

The findings almost parallel those of the child's sibling[6] except for the cerebral cortical lesions in our case. The lesions resemble those described by Oberling and Woringer[2] save for the absence of vacuolization.

Lipid analyses of the liver and spleen were made and reported by Dr. Donald Fairbairn as follows:

A chloroform solution of the total lipids[10] was treated with acetone and magnesium chloride, and the acetone-soluble fraction (triglycerides, sterols) was then washed with water, dried, and weighed. The weight of the acetone-insoluble substances was then obtained by difference. In this fraction total phospholipids were calculated from the phosphorus content,[11] lecithins and cephalins by mild alkaline hydrolysis,[12] and sphingomyelins by difference. Cerebrosides were estimated as the difference between total acetone insolubles and total phospholipids. The results showed that cerebrosides were abundantly present in both liver and spleen, and that the phospholipid content of these organs was unusually small (Table I).

Portions of the acetone-insoluble fraction from both tissues were hydrolyzed in dilute hydrochloric acid,[13] the acid was removed in vacuo, and the hydrolyzate examined qualitatively for monosaccharides by paper chromatography.[14, 15] From the re-

TABLE I. FRACTIONATION OF TOTAL LIPIDS

| FRACTION | SPLEEN % OF DRY WEIGHT | LIVER % OF DRY WEIGHT |
|---|---|---|
| Total lipids | 22.8 | 30.4 |
| Acetone solubles | 7.2 | 8.6 |
| Acetone insolubles (by difference) | 15.6 | 21.8 |
| Total phospholipids | 4.1 | 5.1 |
| Lecithins and cephalins | 3.6 | 4.2 |
| Sphingomyelins (by difference) | 1.1 | 0.9 |
| Cerebrosides (by difference) | 10.9 | 16.6 |
| Cerebrosides (by glucose determination) | 1.7 | 0.3 |

sults it was clear that galactose, the normal carbohydrate component of cerebrosides, was replaced by glucose. This finding is in accord with that of Halliday and associates.[16] In addition, a second reducing substance was observed on the paper in approximately the same amounts as glucose. The RF of this substance, which was not identified, was considerably lower than that of glucose (Table II).

TABLE II. PAPER CHROMATOGRAPHY OF CEREBROSIDE HYDROLYZATE
The solvent used was pyridine:water:butanol (2:1.5:3)

| COMPOUND | RF |
|---|---|
| Galactose | 0.58 |
| Glucose | 0.68 |
| Hydrolyzate (1) | 0.68 (glucose) |
| (2) | 0.53 (unknown) |

The same or similar hydrolyzates were employed for the quantitative determination of reducing (and fermentable) sugar[17] using glucose as a standard. Conversion of the results to terms of cerebrosides gave values for cerebrosides which were only a small fraction of those determined by the difference method (Table I). Although this conflict in results was not resolved, it seems possible that the large cerebroside content arrived at by the difference method may have been an artefact arising from the presence in the acetone-insoluble fraction of large amounts of unidentified (and abnormal) substances.

## COMMENT

Since 1895 Gaucher's lipid disorder has been known as a familial disease. Oberling and Woringer[2, 18] reported five cases among the seven siblings of one family. Groen[19] in 1948 first showed the characteristic Gaucher cells in the bone marrow of an adult patient with the disease and of his father who was apparently healthy, and thus indicated the hereditary mechanism of the disease. None of Groen's cases was in an infant. In 1949 Stransky and Davis-Lawas[5] and in 1951 Stransky and Conchu[20] reported the demonstration of Gaucher cells in the bone marrow of the apparently healthy father of one infant with acute Gaucher's disease and in the apparently healthy mother of another infant similarly afflicted.

An older sibling of the subject of this report had died from the same disease. Apart from these two infants there were no known cases of Gaucher's disease or of "spleen trouble" among two parents, four grandparents, six uncles and aunts, and seven first cousins of the patient. The bone marrow of the father, the mother, and the surviving apparently healthy child showed no Gaucher cells. Blood groups of both parents and of the last two children in the family were identical in detail. There was no parental consanguinity. The frequency of the disease among siblings[2, 5, 18] and its appearance in the offspring of related parents[21] suggest a simple recessive type of inheritance. The finding of the pathologic cells in the marrow of healthy parents of involved children indicates that the pathological gene is present in a "carrier" state. The fact that one

frequently cannot find the Gaucher cells in the marrow of involved patients themselves complicates the question of their detection in the marrow of parent "carriers." The parents of our patient were advised that their healthy son was unlikely to produce affected children unless he married a relative and that any future child they themselves produced would have a 25 per cent chance of being affected.

SUMMARY

A case of acute (infantile) Gaucher's disease is reported in an infant of 3 months, one of three siblings, the eldest of whom likewise died of this disease. Diagnosis was confirmed by splenic puncture. Necropsy findings are described. Chemical analysis of spleen and liver showed the glucosidocerebroside characteristic of this disease. The familial aspect of the disease is discussed.

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# A SUMMER CAMP FOR CHILDREN WITH HEART DISEASE

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DURING the past half century, many summer camps have been organized for healthy children. Camping facilities for children with certain physical handicaps have also been developed. However, children with heart disease have had almost no opportunity to derive the benefits of the type of group-living experienced at camp, or to cultivate at camp the nonathletic and athletic skills within their capacity.

Sprout Lake Camp was founded by the Associated Cardiac Leagues, Inc.* in 1949 exclusively for children with heart disease. It is nonsectarian and no fee is charged. The camp is located in Verbank, Dutchess County, New York, about sixteen miles east of Poughkeepsie. It occupies eighty-eight acres of wooded and cleared land which was formerly an estate. Fig. 1 is a sketch of the camp.

The children live in five wooden, one-story houses built on a relatively flat area of ground which will be referred to as the campus. The adjoining athletic field is also on level ground. There are shower and toilet facilities in the houses, and at the entrances are separated areas for storing raincoats and rubbers. The houses are partitioned to form two "bunks," each of which accommodates about eight children. Nearby is the bunk for nature study and the one for arts and crafts. The latter building is large and modern and has excellent equipment; one of its porches can also serve as an outdoor stage. In the main house are the dining rooms, administrative offices, a library, an auditorium, an indoor play area, rooms for music, newspaper, and photography hobbies, and the infirmary. The latter consists of a large examining and treatment room and two bedrooms with space for eight patients. A hill 560 feet long, with a 7 per cent grade, leads from the main house to that part of the lake where the children swim. In this area the maximum depth of the water is 38 inches.

## THE STAFF

The staff at camp included a director, an assistant director, a dietician, a physician (which was my position in 1951 and 1952), a registered nurse, twenty counsellors, two cooks, two kitchen helpers, five waiters, a caretaker, and a woman in charge of laundry. The counsellors had completed at least one year of college training, and included people who were studying pedagogy, medicine, pharmacy, occupational therapy, and law. Before camp started, the counsellors met twice with the camp director and once with the medical director, who discussed rheumatic fever and heart disease in children and the counsellors' responsi-

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*The organization was formed for this purpose by the members of the following five groups of women: Community Child Welfare League, Ethel Spiegel Welfare League, League for Cardiac Children, Sara Holland League, and Sylvia Parmet Wiener League.

bilities in matters pertaining to the health of the children. During the summer, there were weekly meetings of the entire staff.

### THE CAMPERS

Approximately seventy-five boys and girls, 8 through 12 years of age, were at Sprout Lake Camp in July and another seventy-five in August. Almost all of the campers lived in New York City and many were from underprivileged homes. Three-fourths of the children in 1951 and 1952 were referred to the camp by children's cardiac clinics, the others by private physicians, by teachers, or by the Department of Health of New York City. The referring agencies were asked to recommend children whose functional and therapeutic cardiac classifications* were *IB* through *IIC*, and who had not had rheumatic activity during the preceding nine months nor cardiovascular surgery during the previous six months. The application forms had spaces for a medical history, physical examination, cardiac diagnosis, and so-

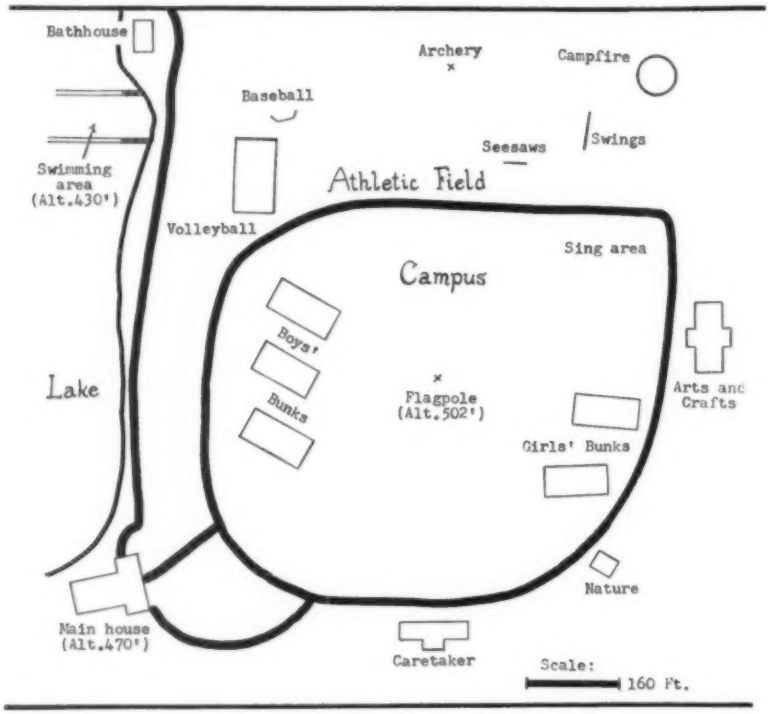


Fig. 1.

*As established by the Criteria Committee of the New York Heart Association, a functional classification of *I* refers to persons with heart disease to whom "ordinary physical activity does not cause discomfort," and *II* refers to patients who subjectively have "slight limitation of physical activity." A therapeutic classification of *A* refers to "patients with cardiac disease whose physical activity need not be restricted," *B*, to those "whose ordinary physical activity need not be restricted, but who should be advised against ususually severe or competitive efforts," and *C*, to those "whose ordinary physical activity should be moderately restricted."

cial history. A preliminary screening of the applications was made by members of the Admissions Committee of the Associated Cardiac Leagues and the camp physician. If they felt that the application indicated that a child would benefit from Sprout Lake Camp, he was referred for an examination by one of the eight members of the Medical Committee, of which Dr. Nathaniel T. Kwit was chairman, to determine whether he met the medical requirements for admission.

The campers in 1951 and 1952 had a number of different kinds of cardiac lesions. In computing the incidence of the various lesions, the figures for the two summers have been combined. Children who were at camp both years (of whom there were fifty-five) were counted twice. One-third of the children had congenital heart disease. Two children had cor pulmonale and two had enlarged hearts as the result of sickle-cell anemia. The rest of the children had had rheumatic fever. Of those with rheumatic heart disease, 62 per cent had mitral insufficiency alone, 17 per cent had mitral insufficiency and stenosis, 6 per cent had only aortic insufficiency, 6 per cent had mitral and aortic insufficiency, 7 per cent had mitral insufficiency and stenosis and aortic insufficiency, and 1 per cent had mitral stenosis and aortic insufficiency.

The varieties of congenital heart disease represented and the number of children who had each were as follows:

Tetralogy of Fallot:
  Postoperative 25
  Unoperated 3
Interauricular septal defect 10
Interventricular septal defect 16
Pulmonary stenosis:
  Postoperative 2
  Unoperated 7
Patent ductus arteriosus (unoperated) 4
Single ventricle 2
Dilated pulmonary artery 2
Subaortic stenosis 4
Coaretation of the aorta:
  Postoperative 1
  Unoperated 1
Transposition of the great vessels 2
Interauricular and interventricular septal defects and overriding aorta 1
Enlarged ascending aorta 1
Type undiagnosed 17

The medical records submitted by the referring agencies indicated that the functional and therapeutic classifications designated for a child depended not only on his cardiac lesion and activity tolerance, but also on their evaluation and interpretation by the examining physician and his opinion about the amount of physical activity advisable for children with heart disease. Statistics concerning these classifications will therefore be omitted, except for mentioning that during the two summers, twenty-six children manifested a greater degree of dyspnea or tiring after running than do normal children, and seventeen children had to walk more slowly than healthy children. (Children who were at camp both years were counted twice).

## THE PROGRAM

The daily program will be given in detail in order to indicate the range of activities and the amount of walking which the children did. The children were awakened at 7:30 A.M., and washed and dressed themselves in the following half hour, after which there were flag-raising, breakfast, and an hour's cleanup. The children made their own beds, swept the floors, and cleaned the basins, and the grounds around the bunks. (Incidentally, the children were assigned to bunks on the basis of their ages.) The entire camp then met for a half hour of group singing. There was one major morning activity which was selected by bunk

groups and consisted of any one of the following: rowing, baseball, volleyball, shooting for baskets, teetherball, craftwork, fishing, going on a cook-out, folk-dancing, music, building a lean-to, or instruction in swimming. During the very hot weather, there was a morning swim for all. A half-hour interval for washing and quiet play preceded dinner, and after dinner there was a "siesta" of an hour and a half. The children lay on their beds during the first half of this rest period and were permitted to read or write letters during the latter half.

The first of the two afternoon activities was a general swim. Including the time required to walk to and from the lake and to change clothing, one and one-quarter hours elapsed. The children were in the water for about a half hour; however, they remained for a shorter period if they felt cold or if the counsellors saw them shiver. Following the swim, milk and cookies were served near the athletic field. Then each child went to the "hobby" which he selected for a one-week period. The hobbies were arts and crafts, nature, music, dramatics, photography, newspaper, folk-dancing, and rowing. There was a half hour wash-up period and flag-lowering before supper which was at 6 P.M.

The entire camp usually participated in the evening activity. Movies were shown once a week. Sometimes the children gave dramatic presentations. There were also quiz programs, a barn dance, various types of treasure hunts (which required walking around the campus), and campfires. Bedtime was 9 P.M.

The activities listed resemble those of healthy campers. Indeed, visitors frequently commented on how like the usual camp program ours was. This probably was primarily the result of our belief that a major function of Sprout Lake was to show its campers how much like healthy youngsters they are. The only general restriction in physical activity at camp was the omission of competitive games. When indicated, further modifications in the activities of individual children were introduced. The staff quickly appreciated the necessity for this, since it was evident that the children varied greatly in their functional capacities from those who had a normal exercise tolerance to those who became dyspneic or tired after a short walk.

In certain sports, such as archery and boating, no modifications were required. Many of the children learned to row. The older children handled a boatful of friends alone; when the younger ones went boating, two children usually rowed together.

Swimming was the favorite sport and differed at Sprout Lake only in that a few children rested more often than healthy children would have. During the past two summers, nineteen children earned Red Cross beginner certificates, fifteen intermediate, sixteen deep water, and thirty-seven swimmer certificates; fourteen children became Junior Lifesavers.

At the time of the weekly hike and picnic lunch, most of the campers went by bunk groups on hikes as long as several miles. It was found necessary to organize a "slow hiking" group for four severely handicapped children during August, 1952. This enabled every child to say that he had gone hiking.

The variations in the way baseball was played exemplify the flexibility of the program. Many of the children

played a normal game except that only a few innings were played and that there was no emphasis on winning for a team. When necessary, the bases were moved closer together to lessen the distances the children ran around the diamond. A couple of boys had never even caught a soft rubber ball. Although they did not play in a game of baseball, they were shown how to catch a ball and how to hold and use a bat. Their surprise and delight in being able to bat a ball a few yards appeared as great as that of healthier boys in making a home run.

Although the *medical supervision* was greater than in most camps, we tried to impress on the children that Sprout Lake was indeed a camp, and not a clinic, hospital, or convalescent home.

Routinely each child had three physical examinations at camp. The purposes of the first one, which was done within forty-eight hours of arrival at camp, were to determine whether a child had any general health problem, communicable disease, or clinical evidence of rheumatic activity; to determine the probable cardiac diagnosis; and to try to find out from him the amount of physical activity to which he was accustomed at home. The counsellors were told about any special features to be watched in individual campers. Two weeks later, each child was re-examined, and an evaluation of his functional capacity, based on the observations of the counsellors and the physician, was made. Observations and suggestions for the referring agencies were recorded. A final examination was made within two days of the child's departure from camp.

Medications which the referring physicians recommended that their patients receive regularly were taken in the bunks. The responsibility for remembering to take the medicine rested with the camper and his counsellor; the camp physician reminded both at intervals. Two children received penicillin prophylactically during 1951, and fourteen children took penicillin or sulfonamides during 1952. Two children took digitalis preparations and two were on anticonvulsant therapy.

It was considered very important to attempt to keep respiratory infections at a minimum. For this reason, no visitors (except professional workers in medical and allied fields) were permitted at camp. The program was such that the children did not become overtired. The counsellors were instructed to see that the children dressed sufficiently warmly, especially in the evenings, and that they wore rubbers whenever the grass was wet. The swimming clothes were changed in the bathhouses, so that the children did not walk or sit around in wet suits. Each bunk had a large tarpaulin which was spread on the ground for the children to sit on at such activities as the morning sing or outdoor evening entertainments.

If a child complained of a sore throat or had even a very mild upper respiratory infection, he was put to bed in the infirmary to give him an extra rest and to try to prevent his bunkmates from becoming ill. Any rheumatic child who developed acute pharyngitis with fever was treated with penicillin intramuscularly for three days followed by oral penicillin for seven days.

The majority of the children's complaints and illnesses were of the minor types encountered in other camps. In addition, one child had a sickle-cell crisis, and four children were believed to have rheumatic activity. One of them was found to have carditis and congestive heart failure on the routine examination made on the day of his arrival at camp. A second child had had chorea for two years; it was felt that the camp program subjected her to more stress than was advisable. Another youngster appeared to have low-grade rheumatic activity (manifested by migratory pains in the extremities, low-grade fever, anorexia, and pallor) which had probably been present for several months, and was fully appreciated only after the child was observed in the infirmary for several days. The fourth child developed chorea and carditis toward the end of the first week in camp. These children were sent home or to hospitals.

## DISCUSSION

One of the major problems we anticipated was the determination of how much physical activity the children could do and should be permitted to do at camp. Although many children with inactive rheumatic heart disease feel able to do whatever healthy children do, there is a difference of opinion among physicians about the advisability of limiting physical activity. Most of the physicians who referred such children to Sprout Lake recommended that the children omit competitive games. Since there were none at camp, it was not necessary to pay special attention to the amount of physical activity of the majority of children who had rheumatic heart disease. The exceptions were a few children with cardiac enlargement who would run around a great deal if guided only by their own desires; an attempt was made to restrict these children to a walking pace when they went from one activity to another.

The children who had congenital defects and had a functional classification of *I* were treated similarly. It was observed that the more severely handicapped children with congenital heart disease were usually self-limited and voluntarily stopped to rest if they became dyspneic or tired. The question of activity regulation was resolved much more easily than had been expected by following two broad policies —omitting competitive games and respecting the need of certain campers to set their own tempo.

Since Sprout Lake has shown that camping is feasible for children with many types of heart disease, it is hoped that increased opportunities for attending camp will be made available to such children both through the founding of other special camps and by permitting more children with heart disease to attend normal camps which are now in existence. Administrators of camps frequently are afraid of accepting any child labeled "cardiac" and are not aware that children with heart disease vary in their degrees of handicap and in the amount of restriction which need be imposed on their activity. Children classified as IA should be able to attend any camp, and those classified as IB might attend camps where athletic activities are not emphasized.

Camp can be even more valuable to a child with heart disease than to a healthy child because it is an environment where an optimistic attitude can be substituted for fears and misconcep-

tions which the child may have about his physical condition. At home he is often reminded of his handicap (real or exaggerated) by parents, siblings, classmates, teachers, and medical personnel, and unwarranted restrictions of his physical exertion may be imposed. Parents have been known to tell a child that he will become severely ill or will die if he disregards the restrictions. It is understandable that parents are greatly alarmed by the idea that there is an organic lesion in their child's heart, but it is unfortunate that they sometimes become so overprotective that they do not permit the child to acquire the ability to perform even the simple routines of daily self-care. It is also regrettable that other youngsters sometimes ridicule and embarrass the child with heart disease because he is different from them in his physical activity and/or in his appearance, due to cyanosis, clubbing, a scar on his chest or coexisting congenital anomalies.

A child with heart disease can be shown at camp that he can participate in and enjoy many of the activities in which healthy children engage. If his functional capacity is less than normal, he can learn what the extent of his physical handicap really is, without an added psychological limitation fostered by anxious adults. The necessary health supervision can be maintained by a friendly and understanding camp staff in such a way that the child is less aware of the guidance than when under parental supervision. Another advantage of the camping season is that it gives the child's parents a rest from being responsible for his welfare; it is probable that this will make the parents more relaxed in their handling of the child when he returns home. It is hoped that the apprehension of the parents will be lessened as they learn what their child was able to do at camp. It should be made clear to them that the child was supervised at his activities and was encouraged to take part in them as a deliberate therapeutic procedure. Although one month is a short span of time, we feel that the benefits the child derives during a camping period can be of permanent value to him and to his family.

## SUMMARY

The physical facilities, program, and medical aspects of a pioneer camp for children with heart disease have been described. The feasibility of camping for children with many types of cardiac pathology has been demonstrated. Its value, especially in fostering the psychological health of the children and their parents, has been discussed. It is urged that an increase in camping opportunities be made available to such children.

# A BRIEF HISTORY OF INFANT FEEDING

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THE problem of infant feeding is one of the most discussed in modern pediatrics. Since the turn of the century, there has been much effort among pediatricians and nutritional experts to devise improved infant formulas and schedules. At the same time, there has been an increasing insistence on the part of doctors that the maternal breast is by far the more preferable source of infant nourishment, and should not be substituted for artificial feeding merely for the sake of convenience or fashion. One might consider this to be a problem specifically belonging to our times, stemming from the great advances in the science of nutrition and techniques of sanitation, and from the pace of modern life, with many women working. However, a study of the history of the subject reveals that, in fact, the discussion of the problems of substitute feedings for infants goes back to some of the first writings on medical subjects. It is interesting to note that the same specific problem of interesting mothers in nursing their babies existed before the modern discoveries in nutrition and hygiene, and in cultures with a tempo entirely different from the present. Discussing a famous poem written in sixteenth century Italy to bemoan the abandonment of maternal breast feeding, an English translator two centuries later says of himself, "Such is the coincidence between the state of manners in Italy in the sixteenth century and England in the eighteenth, that the translator, though intending to accommodate the poem to modern times, has seldom found it expedient to vary from the original in the slightest degree."[1] Had it not been too depressing, he might have noted that the same argument would have been timely as far back as the Egypt of the Pharaohs.

This paper will attempt to give a very brief survey of the medical and popular approaches to infant feeding from antiquity to modern times. It is obvious that in a paper of this length it is impossible to include all of the available material.

## ANTIQUITY

The incidence of recorded historical data on the feeding of infants prior to that of Greek medicine is very meager. With the evolution of the rich and flourishing cultures of the valley of the Nile and of the Tigris and Euphrates, increasing attention to the feeding and development of children became manifest.

There have been no infant feeding bottles discovered among the ruins of the pre-Ptolemaic period in Egypt. At that time, breast feeding was the only nourishment available to the infant. The child was nursed for a period of three years, and only after weaning were any other foods given in quantity.

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However, with the introduction into Egypt of Hellenic culture during the Alexandrian era, the attitudes toward infant feeding were changed. From this period, large numbers of feeding bottles modeled after Greek design are found. The introduction of Greek culture and sophistication influenced the upper classes of Egyptians to abandon nursing their own children. "Definite contracts were made with slave women, who stipulated to nourish the child on milk up to its third year for a definite sum and their living."[2]

A primary indication of the interest given to nursing infants in Babylon is contained in vast numbers of terra-cotta reliefs and figurines from archeological digs, showing the Babylonian mother goddess, Ishtar, nursing her child. Second, the code of Hammurabi, 2250 B.C., contains many laws and instructions for the protection of the mother and infant. For example, if a nurse allowed a suckling to die on her hands and substituted another, her breast was amputated.

### INDIA

The best information we have concerning ancient Indian attitudes toward infant feeding comes from the Brahministic period (1000 to 800 B.C.), during which Indian medicine experienced its golden age. In the Susruta Samhita, second century B.C., one of the three codifications of Brahminical medicine, there is a complete description. The newborn infant was not breast fed until the fourth day after birth. Before this, a small amount of honey was administered to produce the evacuation of the meconium. Specific instructions are given for the selection of a wet nurse, when necessary. Aside from being neither too young nor too old, of sound health and good character, and free from the vices of gambling, debauchery, and daydreaming, she must be "of an affectionate heart, and with all of her children living." There are further careful instructions for the proper care of her own health. In case she suffers a suppression of milk from anger or "lack of affection toward the child," she is to be given a generous diet of rice, barley, wheat, wine, garlic, and lotus stalk to re-establish her equanimity and flow of milk. If the mother or wet nurse is hungry, aggrieved, tired, feverish, pregnant, or has a bad digestion, she is not to be permitted to nurse the child. "Pure and healthy breast milk is thin, cold, clear, the color of a conch-shell, easily miscible with water, neither floating nor sinking, and producing neither froths nor shreds."[3]

### ISRAEL

The source of information for the customs of ancient Israel is the Talmud, the commentary on the five books of the Mosaic law, dating from 536 B.C. This is an aggregation of verbal tradition and law. Its instructions are that the child is to be put to the breast immediately, even before the cutting of the cord. If the child did not nurse, hot coals were held near the mouth to stimulate the facial muscles. As in India, honey was given to facilitate the excretion of the meconium. Generally, a child was suckled for a period of eighteen months to two years. Babies were loved, and a large family was considered to be God's greatest blessing. Nowhere in the history of the Israelites is there evidence of substitutes for maternal feeding, except in cases of necessity. The prophets re-

garded this as a duty of the mother: "Can a woman forget her sucking child, that she should not have compassion on the son of her womb?" (Isaiah xlix:15.) In case the husband of a nursing mother should die, she could not marry again until her child was weaned, lest a new pregnancy interfere with nursing. But if the mother was not able to nurse her child, a wet nurse, usually a slave, could be engaged. The wet nurse was under contract for two to three years, during which time she could do no other work nor nurse any other child, even her own. She was held responsible for the fate of the child, and, if found competent, would be treated with high esteem as a member of the family, like Deborah, the nurse of Rebekah. For the nursing period, no woman was expected to labor much, and she was fed well. There is no mention in the Talmud of nursing bottles, although they were being used in Rome and Alexandria in the same period. Rabbi Joshua held that breast nourishment could continue as many years as desired. The night was divided into three watches, and the baby was to be nursed in the third, before dawn. In cases of arguments between husbands and wives on these matters, the wife should prevail, since hers was the trouble.

### GREECE

During the Homeric period, around 950 B.C., infants who had been deemed worthy of survival were usually nursed by their mothers. Exposure of unwanted or weak babies was common and acceptable. They were flung upon dung heaps, and if found by benevolent persons, could be wet-nursed and brought up as slaves; if not, they were devoured by dogs and wild animals. Wet nurses usually became general housekeepers as well. In a Homeric poem to Demeter we read,

> And truly I could nurse a young infant, and could hold him in my arms, and could spread my master's bed in the recess of the wall, and could manage the works of women.[4]

By the time of Hellenistic Greece, the infants of the better off of Athens were wet-nursed, as a general rule, by slaves, captives, or free women who thus supported their families. Spartan women were preferred because of their famous physical vigor. During this time, the child was given six months or more of breast, and then eighteen months of cow's milk from a nursing bottle. The widespread usage of artificial feeding is evidenced by large numbers of bottles found in children's graves from this period.

Hippocrates, 460-370 B.C., speaks at length on various diseases of children, especially dysenteries and fevers, and congenital deformities of the spine and foot. But in all the discussion of pediatric subjects, there is scarcely one reference to infant nutrition. In the *Aphorisms* he says, "Old persons endure fasting most easily; next adults, young persons not nearly so well, and most especially infants, and of them, such as are of a particularly lively spirit. Growing bodies have the most innate heat; they therefore require the most food, for otherwise their bodies are wasted."[5]

A passing reference to the relation between diet and disease is made in Aristotle's instructions to midwives in his *Historia Animalum,* "Children are very subject to spasm, and especially those who are in a good condition or whose nurses are fat. Wine is injurious in this complaint, and dark

colored wines more than those which are pale, and food which is not fluid, and windy aliments, and stoppage in the bowels.''[6]

ROME

Infant nutrition in Rome followed very closely that of the latter periods in Greece, with the popularity of the wet nurse and of artificial feeding. The wet nurse was now often chosen from Greek slave stock. However, in Rome legislation favored the rearing of large families, and exposure or infanticide, especially of males, was infrequent.

Celsus, who made, perhaps, the only real Roman contribution to medicine, gives few remarks on the diseases of children. In speaking of the condition of ''aptha,'' which many think is thrush or diphtheria, he remarks that the disease is even worse in a suckling. He advises as treatment for this that the nurse should exercise her body, bathe frequently, and foment the breast with hot water. If the child has fever, she must diet and drink plenty of water, otherwise light wine; she must purge herself, and procure emesis if she has phlegm. The babies' ulcers should be anointed with sweet plants.

The most complete pediatric account from antiquity is that of the Greek, Soranus. He studied medicine in Alexandria, and settled in Rome between A.D. 110-130. The following is a part of his ''Compendium'' of infant care.

After the infant has been swaddled and cradeled, it should rest and receive no food at least for the first two days, for the child is apt to be in continual motion during all this time and its body is still amply provided with nourishment derived from the mother, which it must first have time to digest before it is ready for new food. The case is altered should it develop a premature appetite, the signs of which I will explain later. After this pause, something may be prepared for the child to lick up, but never butter, which is difficult to digest and injurious to the stomach. . . . For this purpose, slightly boiled honey is much more to be recommended for everything raw is sharp and produces flatulence; but things cooked too long are constipating in the highest degree, and what is cooked for a moderate length of time cleanses the stomach and the intestines. The mouth of the nurseling is, therefore, to be softly stroked with the finger after which lukewarm honey and water is dribbled into it. In this way, the rich, thick material is diluted, the appetite is increased, since the child will recollect the pleasant taste, the esophagus is opened, the digestion of food proceeds easily after the canal has been cleansed and thus the whole constitution is nourished. . . . During the first twenty days the mother's milk is, as a rule, unfit for consumption by the child, being thick, cheesy and difficult to digest. A wet nurse is preferable.[8]

Soranus gives a description of a test for determining whether the nurse's milk is of the right consisteney and digestibility. This test was perpetuated throughout the next 1500 years, and was mentioned as late as 1752 by William Smellie in the *Treatise on the Theory and Practice of Midwifery*, published in London.

Whether the milk will coagulate properly is determined by the fact that if we put a drop on the fingernail or on a laurel leaf or other smooth surface it slowly spreads, and when shaken, retains the drop-form; for if it flows at once in all directions, it is watery, but if it coheres like honey and does not change its drop-form, it is too thick. We may also make the test by adding twice as much water to a given quantity of milk; the solution will then take place only after a considerable time, and the white color is retained to the last. If solution takes place at once the milk is watery and it can be used still less if it forms a fibrous coagulum like that of serum. In such a condition it is indigestible. But if, after some time, it does not

diffuse and sinks in such a manner that it remains at the bottom when water is poured on it, it is cheesy, thick, and soluble with difficulty.[9]

Galen, A.D. 131-201, contributed little to the subject of infant nutrition, repeating the accepted ideas of Soranus. An interesting note is his warning against nursing the child before or during its bath.

### BYZANTIUM

The period in history dominated by the Byzantine culture, A.D. 476-732, was one of no innovations in medicine. The writers during this period were following after the pattern set by the later Greeks and Romans, particularly Galen and Celsus. Their effort was to compile and summarize all extant medical knowledge. This approach to medical writing was to remain the fashion for the next 1,000 years.

Oribasius, A.D. 325-403, giving a compendium of the earlier Greek physicians' work and many of Aristotle's observations, has long chapters on the rearing of infants, and the choice of a nurse. He repeats verbatim Soranus' fingernail test.

> Meat is bad for infants, also thick soups, as creating phlegm.
>
> Honey is the natural first food; its sweetness is attractive, and it purges the intestines of meconium.
>
> It is very bad for the nurse to eat celery, mint, garlic, and everything of a very desiccative nature, and likewise such as are saltish, acrid, sour, acid, bitter, very heating, or of an offensive smell, as affecting the milk, and inducing epilepsy and pustules in the child.
>
> It is of great consequence to the child that his nurse should have brought forth but a short time before, and that her child had been a male rather than otherwise.
>
> Let her work with her hands and shoulders, let her labour at the mill and the loom, and carry about the child in her arms.[10]

Paul of Aegina, A.D. 625-690, was the last of the great compilers of this age. He makes the choice of a nurse as follows:

> A nurse is to be chosen who is . . . not less than twenty-five nor more than thirty-five. Her chest should be large, as also her breasts. The bad qualities of milk may be thus corrected. If it be too thick, the phlegm ought to be evacuated by vomits, the most proper of which are those of vinegar and honey. Also . . . wild marjoram, hyssop, savoury, shepherd's needle, thyme, the small radish, and old pickle. But if more acrid and thinner than natural, the nurse ought to be relieved from much labour, to be fed upon strong soups, and the flesh of swine, and to be allowed a sodden must and sweet wine. . . . That medicines for the formation of milk are possessed of some efficacy, I am well aware, and yet I do not recommend them in all cases, for they greatly waste the body.[11]

At this period, a child was to be nursed three times daily for six months. Eggs, dilute honey, or wine were then supplementarily allowed in small quantities, and the child was generally weaned after twenty months.

### ISLAM

The Mohammedan world, which experienced its golden age from A.D. 732 to 1100, produced little that was new in medical knowledge. The vast bulk of Moslem medicine was taken over from that which had been collected by the Christian Byzantine compilers. The only major addition to the Greco-Roman ideas was the complicated, arbitrary, and mostly valueless pharmacologic preparations, which were added to the section on treatment. The Koran gives the view that mothers must suckle their children for two full years. They are permitted to employ a wet nurse in case this is impossible. Other standards of infant care are set by the published codes of Mohammedan

ethics. Related to feeding, there are to be found only repeated warnings against feeding wine to infants, which follows the religious taboo on alcoholic beverages. Family feeling was very strong, and the Koran severely threatens practitioners of female infanticide.

### THE MIDDLE AGES

During the long period of the Middle Ages there was practically no addition to the aggregate of the great medical compendiums made in the Byzantine period. It was difficult enough to preserve this from the inroads of barbarianism. Medicine, as a science, remained strictly formalized. However, the introduction of the Christian concepts of the immortality of the soul, family dignity, and the love of children brought about a marked decrease in the abandonment of infants. With the triumph of Christianity in the Roman Empire, there followed a series of government edicts against infanticide: by Constantine, 315-321, Valentinian, 374, and Theodosius, 391. During the fourth to sixth centuries, provisions were made in the Councils of the Church for the protection of abandoned infants and the procuring of wet nurses for them. In 787 Datheus, the Archbishop of Milan, founded the first large home for abandoned infants. Soon such foundling asylums were common in the large centers of medieval Europe.

One of the most interesting and curious approaches to infant feeding had its origin in one of these homes. In the year 1204, after having seen some bodies of unwanted infants which had been thrown into the Tiber, Pope Innocent III dedicated a large section of the hospital Santa Maria in Sassia, located on the Tiber banks, to the care of foundlings. A special door was built into the wall of the hospital for the leaving of children, which could be opened from the street to place an infant in a warm compartment.[12] The number of infants grew, and likewise a large corps of wet nurses. It was found by those in charge that music was an invaluable aid to the health of the nursing infants. All the babies and wet nurses would be brought together in a large room for feeding. Not only did the children become more peaceful and suckle better, but also the nurses' milk was found to flow more freely under the soothing influence of the flute and lute. The music was provided by young boys. Much public interest was aroused in the asylum, and music designed to be played during the nursing hours was composed by the great Palestrina. Later, this led to the training of the children reared in the asylum as musicians. They journeyed over Europe singing concerts, improving musical standards, and gathering funds for foundlings.[13]

During the length of the Middle Ages, breast feeding was everywhere the rule, and the wet nurse was not usually employed when unnecessary. Nursing bottles were unknown.

### THE RENAISSANCE

Although the later Renaissance saw great strides in the evolution of a new science of medicine, the beginnings of this period were not promising. Most medical writers were still mere historians. In Pietro Bagellardo's *De Aegeritudinibus Infantium*, 1472, mothers are directed to "croon a song while rocking the cradle." The first vernacular textbook of pediatrics was compiled by Bartholomaus Metlinger, *Regiment der jungen Kinder*, Augsburg, 1473. Both of these books are essentially the same in teaching as the

work of centuries before. There are lengthy and traditional discussions of infant care and nursing. The milk test of Soranus is given in Metlinger. He follows Avicenna in discussing how the milk is formed in the mother out of the suppressed menstrual blood which runs to the breast through the vessels provided for this. He advises that the mother's milk is unhealthy for fourteen days, and that she should be nursed by a young wolf or have the milk drawn off, while another woman takes her child.

The best wet nurse . . . should be not younger than twenty years and at twenty-five she is at her best. Her own child should be over six weeks old. It is best when she has suckled two or three other children. The time of her delivery should not have been too soon, either with this child or with the others. She should be well built; her face healthy in appearance, tanned; and she should have a strong thick neck, strong broad breasts, not too fat and not too thin, but preferably well formed and fleshy and that do not hang down, not too small but average good size. The wet nurse should have praiseworthy habits. She should not be easily frightened or worried and not small-minded or prone to anger. She should be industrious and careful with the child. She should take care that she does not become pregnant as this is dangerous to the child, as the best blood of the pregnant woman goes to the fetus. In such cases, the child should be weaned. The less the child nurses at this time the better it is for the child. Also the wet nurse should not be diseased.[14]

If she loses her milk, she is directed to eat the udder or bag of goats or sheep, which is held to be an early reference to glandular therapy. Supplementary feeding is to be given as follows:

One should also know about the gruel that is given to it after it has nursed; when the milk of the nurse is good and she has enough the child needs less gruel especially when the nursing agrees with it; when the milk is not good or when the wet nurse is sick or has little milk or the baby does not thrive on the nursing, one should give more gruel. One should be careful not to burn the child by giving it gruel that is too hot as it is an old wife's opinion that if the gruel will not burn a coarse finger it will not burn the tender child.

Further it should be known that children are to be nourished on gruel and milk until they cut their front teeth. One may then give somewhat stronger food, bread soaked in milk or meat soup or pea soup and when they become older one can give lean, well-cooked meat cut very fine but in small quantity, as too much and too strong meat causes worms to grow. The normal time for a child to nurse is two years but during this time it can be allowed other things to drink than the mother's milk and other food, such as gruels. One may also give at this time water to drink or a water that has been once brought to a boil and then allowed to cool, or at times a well-water wine.

. . . but if the child is weaned it should be done in a proper manner so that each day the nursing is discontinued and water given to drink which has been cooked once and allowed to cool, or sugar water made with one ounce of sugar and a measure of water and boiled as long as it will take to cook a hard egg. A bread rind may be cooked in it in order that the child may be strengthened. But if the child is young and it must be weaned, one gives it goats' milk to drink out of a cornucopia or a little jug. The milk is boiled with one quarter part of fine bread and one quarter part sugar and mix it as an apothecary would. When they search for the breast crying the nipples may be painted with myrrh wine or wormwood juice and the child allowed to nurse. It should also be noted that when children are over three years of age it is their nature to eat much. . . . As Hippocrates says, children shall not be disturbed at their meals on account of their growth, and food which disturbs their digestion, that is, too much dry bread and fish, and also wine to drink should not be allowed but the child placed on milk alone, even though, in this time, there is no disease. As Galen says, a bad ordering of life in the young shows itself later on.[15]

An important means of treatment for sick nurslings is to bleed the wet nurse if she is well developed and rosy, or to purge her if she is pale.

By the late fifteenth and sixteenth centuries, all types of artificial feeding had come into vogue. Children were given cow's milk or goat's milk from sucking horns (animals' horns with one open end), sucking cans with cloth nipples, bottles, and spoons. The sucking can was of varied shape, sometimes conforming to that of the breast, sometimes an hourglass, or bell. They were crudely made from pottery. Sometimes sugar lumps and bread were held for sucking in a piece of linen that had been pulled into the shape of a nipple.

Another interesting feature of the late Renaissance is the fashion of poems on infant hygiene. Didactic poetry, one of the earliest forms of verse, found in Homer and in the writings of other Greeks and Romans, became fashionable at this time through the revival of ancient learning. One of the most famous of these was written by Tansillo, a professional soldier who was born about 1510. It is called "The Nurse." Here are a few verses from this poem, referred to earlier as arguing the cruelty of mothers in not nursing their own babies.

What fury hostile to the human kind
First led from nature's path the female mind
Th' ingenuous sense by fashion's laws repressed,
And to a babe denied its mother's breast?

. . . . .

O crime! with herbs and drugs of essence high
The sacred fountains of the breast to dry,
Pour back on Nature's self the balmy tide
Which Nature's God for infancy supplied!

. . . . .

To seek a nurse ye traced the country round
At length the mercenary aid is found—
Some wretch of vulgar birth and conduct frail;
Some known offender, flagrant from the jail;
In mind an idiot, or depraved of life,
A shameless strumpet or impoverished wife;
Or be she brown or black, or fresh or fair,
Or to the mother no resemblance bear,
She brings, it seems, a full and flowing breast—
Enough—your care excuses all the rest.

Tansillo believed that mental and moral attitudes were conveyed in the breast milk. He also discusses the much greater danger that the most deadly of the social diseases may be conveyed from the loose moral standards of the wet nurse to the innocent child.

Say, is there one with human feeling fraught
Can bear to think, nor sicken at the thought
That whilst her babe, with unpolluted lips
As nature asks, the vital fountain sips;
Whilst yet its pure and sainted shrine within
Rests the young mind, unconscious of a sin,
He with his daily nutriment should drain
That dread disease which fires the wanton's vein,
Sent as the fiercest messenger of God,
O'er lawless love to wave his scorpion rod?[16]

This poem was addressed to the aristocracy, as there was as yet no danger in the lower classes of not nursing their offspring, except to take jobs as wet nurses. Some historians remark the difference in the fat cherubs of the paintings of this period, children of average people, from the rachitic-looking infants of the later German and Flemish masters, when feeding of artificial foods was universal.

A similar poem attained great popularity after 1584, being translated from the Latin into eleven vernacular languages. This was Scevole de Sainte Marthe's *Paedotrophia*.

## THE SEVENTEENTH AND EIGHTEENTH CENTURIES

The seventeenth century was outstanding in the history of literature, philosophy, and the arts. It was also an age marked by the rapid expansion of science. Following the monumental work of Harvey, 1616, the science of medicine began to expand rapidly.

Such names as Hooke, Vesalius, Leeuwenhoek, Malpighi, and Sydenham belong to this epoch.

However, with all of these advances in science, seventeenth century Europe knew untold cruelty to children and unparalleled numbers of infant mortalities. In Paris and in London the abandoning of infants in sewers and alleys became so common as to hardly give scandal. Abandoned infants would sometimes be found and their limbs mutilated by beggars who wished to use them in appealing for sympathy. By the middle of the century the religious authorities of Paris had moved to increase foundling hospitals. But of 2,000 infants placed in one of them, 75 per cent died within the first three months. Blame for this is attributable to the crowding of the city, poor sanitation, and such widespread ignorance about infant nutrition that babies were often starved to death on indigestible foods. Mass abandonment of maternal breast feeding was now the rule. Wet nurses and "dry nursing" (nonbreast foods) were substituted.

The two dry-nursing preparations generally in use were pap and panada. Pap usually consisted of flour or bread cooked in water, seldom with the addition of animal milk. Panada was a mixture of flour, cereal, or bread, cooked in a broth, and generally combined with butter, or occasionally milk. The first recorded mention of these means of feeding dates from 1465, but no vogue in them occurred during the fifteenth or sixteenth century. Nutritional deficiencies and rickets became widespread, following the feeding of pap and panada. Ettmüller described the conventional method of feeding pap in 1698. "The nurses in taking it into their mouths dilute it with their saliva, and place it, after that, in the infant's mouth. Finally, to better dilute the pap and facilitate its digestion, they give them the breast."[17] The quantity of pap fed was usually large, one and a half to two quarts per day. This resulted in terrible bloating. Pap and panada were fed to babies by means of spoons and pap boats. These latter were sometimes a mere pewter dish with a narrow lip to be placed in the baby's mouth. Other pap boats consisted of a large spoon having a hinged cover mounted on a hollow handle—the speed of feeding to be controlled by pressure on the hinge of the cover and by blowing, if necessary, through the hollow handle.

Although nursing flasks made of pewter have also been found, the use of cow's milk was at this time limited, for it was found in the cities that its exclusive use led to precipitous death by "the watery gripes." In crowded London, cows and other animals were usually kept in filthy cellars. Walter Harris in the seventeenth century and John Pachey in the eighteenth century warned emphatically against the use of cow's milk.

The literature on infant care of these two centuries contains endless recipes for the preparation of paps and panadas. Ettmüller "detests above all the use of crude flour which having been mixed and cooked with water or milk and reduced to the form of a paste, gives only a viscous and crude paste more proper to binders to bind their books than to the nourishment of infants."[18] He recommends instead white bread dried and crushed, cooked with milk or water, to which is added a little pulverized anise seed. Brouzet, 1754, recommends the pap made from bread "lightly boiled in

beer or wine, with meat and sugar added, reduced to a mucilaginous consistency." Some instructions for making panada from 1783 are as follows: "One puts the mess to boil in a glazed earthen pot which is used only for this purpose and cooks well over a small fire stirring gently with a spoon. The crèmes of rice, barley, oats, semolina, and vermicelli are the farinaceous substances which are most proper . . . "[19]

These preparations were early used as the sole feedings for abandoned infants or the children of the sick poor. They were also used for supplementary feeding to prepare for weanings, and many pediatricians of the eighteenth century recommended this. Harris in 1742 states, "From some sort of active ferment in their stomach, their appetite is so voracious that liquids alone are not able to satisfy them. It must either be blunted with some oily substance such as butter, or the child must be nourished with panada, hasty pudding, or the like, which stay a considerable time in the stomach."[20]

There were, however, some writers of this period who were outspoken in opposition to all artificial feedings for infants. Von Rosenstein, in 1776, says, "Meal pap is never to be given to any child. It is too gluey, tenacious, and slimy a food, and causes obstructions in the mesentery, hardness of the stomach, acidities, wind, and many other indispositions by which we lose at least half our children."[21] DeClaubry in 1783 stated, "Pap is the most dangerous of all the foods for infants, that it has caused to perish a great number, or has rendered them infirm and diseased for their whole lives."[22] However, in spite of the very common medical opinion against the abuses of exclusive pap feedings, in 1813 James Hamilton wrote, "Panada and pap be now almost universally used for the first food of infants as a substitute for the mother's milk."[23]

A listing in the *Ladies' Library*, a popular magazine of 1714-1772, gives an interesting account of a lay opinion on child feeding.

> Regarding food, it is advised that children never be given flesh for the first three or four years, and after that, not more than once a day. Breakfast and supper should consist of either milk, water-gruel, flummery, milk-pottage, or a good piece of brown bread. Plain, dry bread is considered the ideal food, because it is sufficiently nourishing yet unpalatable enough to discourage gluttony. Since they over-stimulate the appetite, spices or salt are not to be used. We are told that it is advisable to vary the time for meals each day, because otherwise the stomach will come to expect food at a definite time. Should it be disappointed, peevishness, excess appetite, or loss of appetite results. Fruit is not good. Children, though, are not to be forbidden all fruits, for such a course would result in bribery of servants or some other surreptitious device for obtaining them. Small beer should be the boy's one drink, and he should receive this only after eating dry bread. The bread serves the double purpose of preventing too much drinking and furnishing a time interval in which the overheated body may cool off.[21]

By the middle of the eighteenth century, the infant mortality rates of Paris and London rose even higher. This was not so much the result of the widespread epidemics in cities of that time, as of the terrible abuses which surrounded the unwillingness of mothers to nurse, and the wet-nurse system. As the industrialization of Europe progressed, many of the poor women were obliged to neglect their children to earn a livelihood. The situ-

ation is described by Lenoir, Lieutenant General of Police in the Paris of 1780, as follows:

> One may estimate at from 20 to 21 thousand the number of infants born annually in Paris. One-thirtieth at the most are nursed at the mother's breast, an equal number is nursed in the parental home; two or three thousand, who pertain to the well-to-do class, are placed in the suburbs and surrounding territory with nurses of whose integrity the parents have assured themselves, and whose fees are greater on account of their proximity and their convenience.[22]

And the rest? The other 80 per cent were those subject to abuses, crimes which frequent legislation was not able to correct. Many young women were led by the high pay of wet nurses to have illegitimate children and abandon them at a baby farm or foundling hospital. The mortality rate in these places was appalling. Of 10,272 infants admitted to the Dublin Foundling Hospital between 1775-1796, only 45 survived, a mortality rate of 99.6 per cent. "Death from want of breast milk" was the common entry in the records.

Agents known as *meneurs* recruited the wet nurses for the city of Paris, traveling about the countryside, making contracts with lactating women. They would take along a wagon to transport such women to Paris, either to remain there or to fetch the baby. Numerous laws were passed to govern this traffic. For example, nurses were forbidden to take more than one child at a time, and under strict penalty the *meneurs* could not transport infants without nurses to feed them. By 1784 the abuses were nevertheless so widespread and the number of abandoned infants also so large that propaganda posters were printed by the government to encourage maternal nursing.

Likewise, the doctors spoke out against the wet-nurse traffic. In the excellent *De morbis acutis infantum* of Walter Harris, 1647-1732, outstanding pediatrician of his century, it is regretted that so many "Ladies of Quality" do not nurse their babies in order that they may have "more Time to dress, receive, and pay Visits, attend public Shews and spend the Night at their beloved Cards." Again, William Cadogan, 1711-1797, physician to the foundling hospital in London and a Fellow of the Royal Society, criticizes violently mothers who refuse to nurse their own flesh and blood. He also condemns dry nursing (pap and panada). The *Ladies' Library* of 1714 remarks, "Strange nurses have no motive for safeguarding the young one's health, for if he dies, another job awaits them. In several of the towns and villages about London where this trade of nursing is chiefly driven, hardly one in five of these children lives out the year."[23]

### MODERN PERIOD

There was a tremendous flowering of interest in children's diseases, nutritional deficiencies, and infant feeding in the nineteenth century. However, the abuses of the seventeenth and eighteenth centuries continued in large measure, as the continued high infant mortality indicates. This existed in spite of improved hygienic conditions, and must be attributed to maternal unwillingness to nurse. During the siege of Paris, 1870-1871, the death rate of the total population was doubled, but the infant death rate dropped. This is interpreted as indicating that when the mothers of Paris were no longer able to procure artificial food or wet nurses from the provinces, and were forced to nurse their own infants, these had a

much better opportunity for survival. There was, however, some improvement in the nineteenth century over the preceding ones in percentage of mother-nursed babies. Also, in England, cruelties and abuses of infants and children resulting from industrialization were given attention and some corrective measures taken after the writings of Charles Dickens and others inspired sympathy for them.

It is impossible to mention all the vast throng of modern contributors to the advancement of infant welfare, once interest was aroused, but a few who made important contributions to the spread of improved ideas on infant nutrition will be mentioned. Andre Donne, 1801-1878, published an important treatise on milk, and another, "Conseils to Mothers and Families on the Rearing of Infants." Charles West of London was the author of a momentous pediatric treatise in 1844, based on nearly 200 clinical cases and 600 post mortems, an unusual and scientific departure from the type of pediatric literature of the past. This work contains an interesting table showing the composition of different animals' milks, and he opines that if artificial feeding is necessary, asses' milk is the best. He believes breast feeding to be the most important preventive of infantile diarrhea and tuberculosis. Philippe Biedert, 1847-1916, was one of the founders of the German Society of Pediatrics. He is considered to be the originator of the scientific study of artificial infant feeding. After analyzing the composition of human milk, he set forth in his volume, *Das Kind*, that cow casein is less digestible than the casein of human milk, and suggests that instead of cow's milk, a series of graduated mixtures of cow's cream, water, and milk sugar be used. Otto Heubner, 1843-1926, who is held to be the greatest of modern German pediatricians, was the first to found the calculation of infant diets on their caloric values. Janet-Elizabeth Lane-Claypon, a graduate of the London School of Medicine for Women, made vital investigations of milk, and her book, *Milk and Its Hygiene*, 1916, contributed much toward the acceptance of hygienic methods in the preparation of formulas. The greatest American in the pediatrics of this era was Abraham Jacobi, who came to New York in 1853 from Westphalia. His interests lay in midwifery, child dentition, intestinal diseases of infancy, therapeutics of infancy and childhood, and infant diets. He wrote with much force, and criticized with strong sarcasm the abuses still prevalent in artificial feeding.

> Jacobi's teaching in regard to infant nutrition is simple: mother's milk first and foremost, raw unpasteurized cow's milk never, but corrected by cereal decoctions and salt; the use of cane sugar in place of milk sugar, which is different in human and cow's milk and frequently adulterated. A high percentage of fat is adjudged harmful, and a monotonous diet is especially to be avoided, as leading to scurvy, rickets and other deficiency diseases. One by one, the practical bedside physician and the laboratory specialist alike have come around to the substance of these views.[24]

The science of infantile nutritional diseases did not truly begin until the middle of the nineteenth century, when investigations into the chemistry of foods, including mother's milk, were commenced. However, the approach to these diseases did not change at once; the emphasis long remained on drug therapy rather than on diet correction. The writings of Biedert and Jacobi helped to bring about the more correct emphasis.

Friedrich Ahlfeld of Leipzig in 1878 first suggested the weighing of infants as an aid to more scientific approach to their growth and metabolism. His work was established on basic data contributed by several women physicians who plotted weight and growth curves on their own nursing infants. The concept of "nutritive requirement" of the suckling child was derived from this idea. Voit and Pettenkofer, in estimating the amounts of proteins, fats, and carbohydrates metabolized in the body by a special respiration chamber in 1861, paved the way to a new understanding of nutritional and caloric balance. Max Rubner applied calorimetry to metabolism. Together with Heubner in 1898 he published a famous monograph on the average daily food requirements of the normal and subnormal infant, which is the foundation of all the more modern work.

In the period following, we find the twentieth century contributors investigating all aspects of infant feeding. Heinrich Finkelstein of Berlin published an outstanding monograph in 1904 on the nutritional care of foundlings. A massive treatise on infant nutrition was published in London by Arthur Keller in 1906. He pointed out that breast-fed infants retain more phosphorus than bottle-fed ones. In 1910 Langstein of the University of Berlin collaborated with L. F. Meyer to produce what is generally considered to be the most comprehensive and intelligible work on infant nutrition and metabolism up to that time. Meyer, one of the pupils of Finkelstein, studied the effects of sugar on infants. He also demonstrated that nitrogen was retained for tissue building in fasting infants, and that normal babies are able to digest fats.

Thomas Morgan Rotch, 1849-1914, a Philadelphian, was the first professor of pediatrics at Harvard University. He introduced the method of varying the amounts of fat, carbohydrates, and sugar in the milk according to the metabolic needs of different babies. John Howland of New York, professor of pediatrics successively at Washington University in St. Louis and at Johns Hopkins, has been outstanding in this field. He substituted direct calorimetry in the study of metabolism of sleeping children, 1910-1911, and in 1913 he perfected a formula for estimating the relationship of the area of body surface to infant metabolism.

With the introduction in the latter nineteenth century of the pasteurization of milk, and the understanding of the sanitary handling and preservation of it, cow's milk became increasingly popular for artificial feeding. Along with this, the careful scientific studies of infantile nutritional needs, vitamins and minerals, and of nutritional diseases added up to increase the popularity of artificial feeding. Thus assured of a scientifically adequate formula combined with hygienically pure milk, the vogue of artificial feeding became and is now more widespread than ever before in history.

However, once again voices in the wilderness are being heard urging the return to the maternal breast. This time, the psychologists join the pediatricians in the cause. With both theoretical considerations and clinical observation of behavior problems in children, there is a mass of evidence that breast feeding or the lack of it has some relation to a strong psychological function. The child is given a sense of love and being wanted by closeness to its mother. Conversely, there is a stronger maternal feeling toward a

child which has been fed at the breast.

There is also a mounting number of studies which show that there is a differential in the infant mortality rates between artificially and breast-fed babies, no matter how carefully and correctly formulas are prepared. Whitney, 1920, Haley, 1920, and Hughes, 1923, in their epidemiological studies of infant mortality rates "all found that the artificially fed infants had a mortality rate of four to five times that of the exclusively breast fed under the same conditions."[25] Sedgwick and Fleishner, 1921, attribute the great decline of infant mortalities in Minneapolis then current to a campaign which was to induce mothers to nurse their own babies. In 1935, Grulee, Sanford, and Schwartz, with a study of 20,000 infants, again demonstrated the definite protective value of mother's milk in forestalling the diseases of early infancy.[26] Perhaps the present crusaders may take courage from their medical predecessors in this age-old concern.

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# MEIGS' SYNDROME

## A Report of a Case in a Child

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IN 1937, Meigs and Cass[1] described a syndrome which was characterized by ascites, hydrothorax, and ovarian tumor. They reported on a review of seven cases at that time.

The syndrome was reported in the literature in detail by Nora and Davison[2] in 1947, when they reviewed the thirty-seven previously reported cases and added their own. Since 1947, the following cases were reported: Liu and associates[3] four cases in 1949, Beresford and Aidin[4] one case in 1950, Stearns[5] one case in 1951, and Hilliard and co-workers[6] one case in 1953.

This syndrome more generally is associated with benign tumors of the ovary but cases of malignant tumors have been reported. The article by Meigs associated the syndrome with the fibroma of the ovary.

The importance of this syndrome is that its signs and symptoms simulate those of cardiac, renal, or liver disease, or tuberculous peritonitis. There are also reported cases confused with incurable malignancies in the abdomen. This syndrome is important to recognize because surgical removal of the tumor will affect removal of the effusions and in many cases a cure. The exact reasons for the occurrence of the effusion in the thorax is still undecided.

Of the patients reviewed in the literature, the eldest reported was 77 years old and the youngest 31 years old. The average age of the group was 50 years.

The purpose of this paper is to present a case that occurred in a 9-year-old girl so that the possibility of this syndrome may be given diagnostic consideration in the pediatric age.

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### CASE REPORT

This 9-year-old white female was admitted to the hospital because of a swollen abdomen that had been present for one week. Three weeks before admission the patient had an upper respiratory infection and two weeks before admission had complained of some pain in the left breast. One week before admission, the patient experienced colicky pain in the lower abdomen and her abdomen began to swell.

The past history revealed that the patient was hospitalized one year previously because of pain in the lower abdomen, nausea, and vomiting. She was discharged after three days with a diagnosis of gastroenteritis.

The family history revealed that a grandfather had died of tuberculosis. The mother, father, and one brother were living and well.

On admission, a physical examination revealed a thin, pale, anxious child with a greatly distended abdomen. Her temperature was 100° F. The eyes, ears, nose, and throat were essentially normal. The examination of the lungs revealed all areas were resonant and no râles were heard. The left breast was slightly tender. Heart tones were normal. The abdomen was uniformly distended with fluid. It was tight and no masses were palpable. It was tender in both lower quadrants. There was no edema of the extremities. Rectal examination was negative, except for tenderness and fullness.

On admission, the white blood count was 14,100 with 6 stabs, 70 polymorphonuclears, 21 lymphocytes, 2 monocytes, and 1 eosinophil. The red blood count was 3,800,000 with 11.5 grams of hemoglobin. The urinalysis showed a

trace of albumin and 8 to 10 red blood cells per high-power field.

An abdominal paracentesis was done and 250 c.c. of serosanguineous fluid was removed.

An x-ray of the chest (Fig. 1) showed no evidence of pathology. The diaphragms were elevated secondary to the intra-abdominal pressure. The abdominal film showed evidence of generalized ascites and a slightly enlarged spleen.

The following laboratory findings were reported: All febrile agglutinations were negative. Plasma proteins were 5.77 grams per 100 ml. of serum, albumin 4.01 grams, globulin 1.76 grams. Blood chlorides 325 mg., sodium 296 mg., nonprotein nitrogen 30 mg., cephalin flocculation 3 plus, thymol turbidity 2 units. The ascitic fluid had a total protein of 5 grams per cent. A stain of the fluid for tubercle bacilli was negative. A culture on Petragnani's medium and a guinea pig inoculation were reported negative at a later date. Repeated urinalyses were reported negative.

The patient's temperature fluctuated between 99° and 103° F. A transfusion was stopped after 450 c.c. because of beginning urticaria. This cleared up promptly.

Antibiotics were given and the patient was maintained mainly on intravenous and subcutaneous fluids for the first week in the hospital. The abdomen remained tight and distended. On the seventh hospital day the patient became dyspneic. Physical examination and x-ray (Fig. 2) revealed pleural effusion in the right chest cavity. Thoracentesis was done and 550 c.c. of serosanguineous fluid was removed from the right chest with relief of the dyspnea. The following day dyspnea recurred and 600 c.c. of fluid was again removed from the right chest. X-ray the following day again revealed an increase in the fluid in the right side with early accumulation of fluid on the left side. A repeated tap recovered 750 c.c. fluid from the right chest. At this time a large localized mass was palpated in the lower left quadrant of the abdomen. The following day 450 c.c. more fluid was removed from the right pleural space. A blood transfusion was started and the patient was taken to surgery.

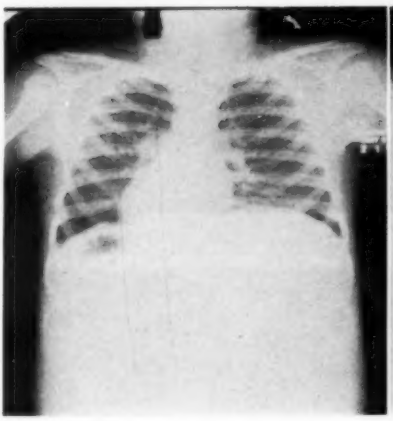

Fig. 1.

Fig. 2.

Fig. 1.—Lung fields normal. Abdomen distended with fluid.
Fig. 2.—Pleural effusion on the right.

Under local anesthesia (1 per cent Novocain) a right rectus incision was made. After removal of the ascitic fluid a large mass was found occupying most of the lower abdominal cavity. The mass was attached to the left ad-

nexa. The mass plus the left tube was removed. The patient was returned to the ward in good condition.

The specimen consisted of an encapsulated tumor rising from the left ovary. It weighed 990 grams and measured 15 x 10 x 8 cm. in size. The cut surface revealed slight cystic degeneration and some hemorrhagic infarction. The noninfarcted tissue was light tan and soft.

Microscopic sections were made from different areas of the tumor (Figs. 3 and 4). The examination revealed a tumor composed of both granulosa- and theca-cell elements. It was well encapsulated by fibrous tissue. Most of the cells were polyhedral with a mod-

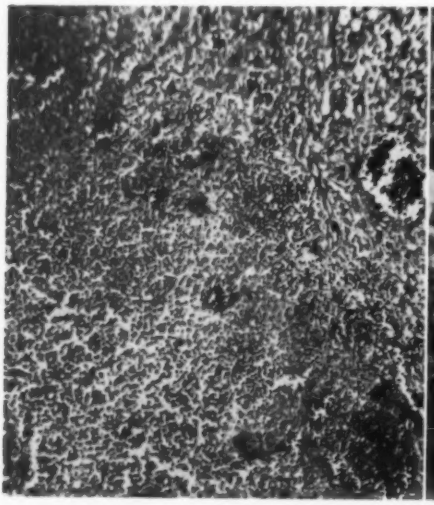

Fig. 3.—(×100, reduced ⅙.)

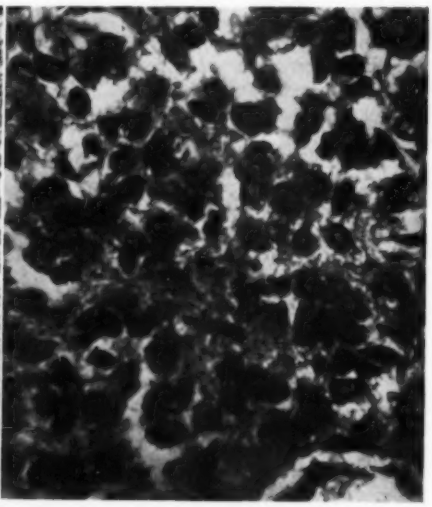

Fig. 4.—(×500, reduced ⅙.)

Fig. 5.

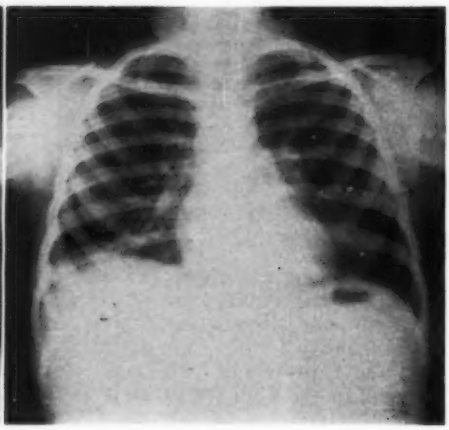

Fig. 6.

Fig. 5.—Left effusion cleared. Effusion up to level of fifth rib on the right.
Fig. 6.—Right effusion almost completely cleared.

erate amount of eosinophilic cytoplasm and had a round or oval, deeply but uniformly stained nuclei. The cells appeared in sheets. Masson stain confirmed the lack of fibrous stroma. A few of the cells showed the presence of fat droplets in their cytoplasm by the use of Sudan III and oil red 0 stains. This indicated theca-cell elements. Some areas showed a few mitoses, while in others mitoses were absent.

The patient's temperature rose to 101° F. on the first and second postoperative days, but then returned to normal and remained so throughout convalescence. An x-ray (Fig. 5) taken on the third postoperative day revealed that the fluid on the left had cleared completely and on the right extended up to the level of the fifth rib. No dyspnea was present. The course following surgery was completely free of complications. The patient was discharged on the ninth postoperative day. An x-ray (Fig. 6) at the time of discharge showed almost complete disappearance of the fluid from the right pleural space.

The patient was checked regularly and at the last examination, which was one year following surgery, there was no evidence of any recurrence.

## DISCUSSION

This tumor was considered a functional feminizing type. Whether this is a benign or malignant tumor is open to question. It is difficult to forecast the outcome. Death from recurrences in unilateral tumors is less frequent than when they are bilateral. Recurrence of ascites usually means a recurrence of the tumor, and if associated with hydrothorax, the prognosis is poor. Diddle[7] in a recent analysis of thirty-five patients and extensive review of the literature states: "Since it is difficult to ascertain the probable outcome for women with feminizing neoplasms and since those tumors that are malignant metastasize in the same manner as other ovarian cancers, total hysterectomy with bilateral salpingo-oophorectomy is the treatment of choice in older patients. Less formidable procedures may be recommended in the prepubertal and reproductive periods of life, provided the neoplasm is well encapsulated. Even then the prognosis must be guarded because fatal recurrences are recorded even among young patients. Feminizing ovarian tumors are unusually radiosensitive. Palliative irradiation is advised in cases in which there are metastases. On the other hand, it appears doubtful that curative effects can be obtained by this form of treatment. Encapsulation offers a better prognosis." This lesion was encapsulated.

This tumor was diagnosed as a functional granulosa- and theca-cell tumor of the ovary. The diagnosis was confirmed by the Armed Forces Institute of Pathology. Their number for this case is 512101.

## SUMMARY

A case of Meigs' syndrome is reported that occurred in a 9-year-old female child. The clearing of the effusions from the abdominal and chest cavities following surgery with removal of the tumor is shown graphically by the x-rays.

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# PAROXYSMAL AURICULAR TACHYCARDIA ASSOCIATED WITH WOLFF-PARKINSON-WHITE SYNDROME IN A NEWBORN INFANT

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SINCE Hubbard[1] first described the syndrome in his classic paper in 1941, numerous articles on paroxysmal auricular tachycardia have appeared in the pediatric literature.[2-5] In 1930, Wolff, Parkinson, and White[6] reported the association of paroxysms of rapid heart action with a short P-R interval and a prolonged QRS interval in the electrocardiograms of healthy young adults. These electrocardiographic defects, subsequently given the name of Wolff-Parkinson-White syndrome, were not observed in infants until 1946 when Bodlander[7] reported them. Oglesby and Harrison[8] reported the syndrome in a 5-week-old infant and reviewed five other cases[9, 10] in the literature.

Paroxysmal auricular tachycardia is a diagnosis that must be considered when one is confronted with the problem of cyanosis in the newborn infant. Hubbard[1] stressed the importance of its early recognition in infants since congestive failure usually supervenes within a short period of time.

In the case reported in this paper, paroxysmal tachycardia associated with the Wolff-Parkinson-White syndrome was first noted in the infant when he was 48 hours old; it was probably present twenty-four hours before. After digitalization, there was an uneventful recovery. The case of a 10-day-old infant reported by Silverman and Werner[11] ended in congestive failure despite treatment with digitalis, Mecholyl, and oxygen.

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## CASE REPORT

J. O'H., a white male infant, was admitted to The Boston Floating Hospital at 48 hours of age because of cyanosis and rapid respiration. The infant was born of a para v gravida v mother after an uneventful pregnancy. Labor was two hours in duration. Delivery was from below and no instruments were used. The birth weight was 9 pounds 15 ounces. Examination of the infant after delivery revealed no abnormalities. At 12 hours of age the infant was started on glucose and water feedings.

At 24 hours of age the infant was reported to have spells of cyanosis and rapid breathing. At 48 hours of age, because of continued episodes of cyanosis and rapid respirations, the infant was referred to The Boston Floating Hospital.

On admission, physical examination revealed a well-developed and well-nourished large white male infant who was cyanotic about the face, arms, and legs, and had a generally dusky color. Respirations were 100 per minute, rapid and shallow. The radial pulse was over 180 per minute and difficult to count. Petechiae were noted on the face and neck. The lungs were resonant to percussion and transient râles were heard on auscultation at the right base. The heart sounds were muffled and of poor quality. The heart rate was over 100 per minute. No murmurs were noted except for a questionable systolic one at the apex. The physical examination revealed no other abnormalities. Slight edema of the extremities was noted.

The infant was placed in an Isolette with constant oxygen and humidity. As tachycardia persisted, obvious signs of congestive failure soon became evident. An electrocardiogram taken soon after admission revealed a supraventricular tachycardia with a rate of 226 per minute. The diagnosis of supraventricular tachycardia accompanied by congestive failure was made. (Fig. 1.)

The infant was given 0.05 mg. of digitoxin intravenously and 0.05 mg. intramuscularly, followed by a maintenance dose of 0.01 mg. by mouth twice daily; within twenty-four hours after digitalization, oral feedings of glucose were started. The general condition of the infant improved. The heart rate dropped to 160 per minute and the respiratory rate dropped to 50 to 60 per minute. Cyanosis disappeared.

At this time a Grade 3 systolic murmur was heard all over the precordium. X-ray and fluoroscopic studies on the second hospital day revealed a generalized cardiac enlargement. Electrocardiograms on the third hospital day revealed the

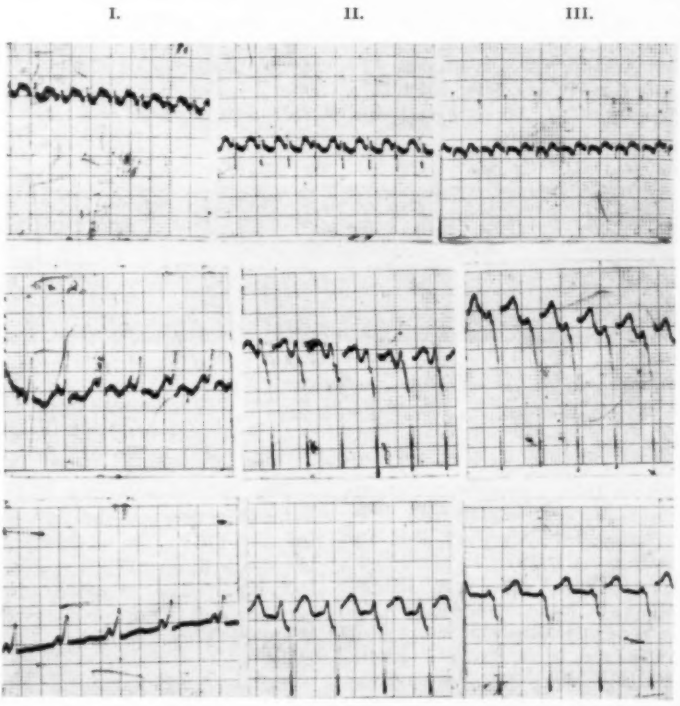


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Electrocardiogram taken on admission May 26, 1952. Auricular rate, 226; ventricular rate, 226; QRS normal; electrical axis, right; rhythm, supraventricular tachycardia.

Fig. 2.—Electrocardiogram taken day after admission and on digitalis therapy. Auricular rate, 164; ventricular rate, 164; P-R, 0.07 sec.; QRS, 0.08 sec.; rhythm, sinus tachycardia; electrical axis, left; S-T depressed in Lead I, $aV_L$, $V_{3R}$-$V_4$; S-T elevated in Lead III, $aV_F$, $V_6$; T inverted in Lead I, $aV_L$, $V_{3R}$-$V_4$; T upright in Leads II, III, $aV_F$, $V_6$. Conclusion: marked left axis deviation in presence of cyanosis consistent with tricuspid atresia or other congenital disorder. Wolff-Parkinson-White syndrome suspected.

Fig. 3.—Electrocardiogram taken twelve days after admission plus when digitalis therapy had been discontinued. Auricular rate, 122; ventricular rate, 122; rhythm, sinus tachycardia; electrical axis, left; short P-R delta wave now more pronounced since previous reading. P-R, 0.07 sec.; QRS, 0.10 sec. Conclusion: abnormal electrocardiogram due to marked left axis deviation, S-T and T changes, and Wolff-Parkinson-White syndrome.

following: auricular rate, 164; ventricular rate, 164; the P-R interval 0.07 sec.; QRS, 0.08 sec.; rhythm, sinus tachycardia; left electrical axis; S-T depressed in Lead I, $aV_L$, $V_{3R}$, and $V_4$; S-T elevated in Lead III, $aV_F$, and $V_6$. Conclusion: extreme axis deviation; ? Wolff-Parkinson-White syndrome. (Fig. 2.)

On the third hospital day, two days after digitalis therapy was instituted, the liver edge that had been palpable 3 cm. below the right costal margin was now palpable 1 cm. below the right costal margin.

Digitalis was discontinued on the eleventh hospital day. On the fourteenth hospital day, one day prior to discharge, the pulse rate was 120 per minute, and the respiratory rate was 40 per minute. An electrocardiogram at this time showed an auricular rate of 122; ventricular rate, 122; rhythm, sinus tachycardia; P-R interval, 0.07 sec.; QRS, 0.10 sec.; Q-T, 0.42 sec.; electrical axis, left. Slowing of the rate was noticed since the previous readings and the short P-R delta wave was now more evident. These findings were felt to be compatible with the Wolff-Parkinson-White syndrome. (Fig. 3.)

At the time of discharge, on the sixteenth hospital day, the infant's general condition was good. The pulse rate was 120 per minute and the respiratory rate was 30 per minute. The murmur, which had previously been a Grade 3 harsh-blowing systolic murmur heard over the entire precordium, was barely audible on discharge.

*Laboratory Data.*—The white blood cell count on admission was 9,200 per cubic millimeter, red blood cells 4,940,000 per cubic millimeter, and the hemoglobin was 19.6 Gm. per 100 c.c. On the day of discharge the white blood cell count was 10,000 per cubic millimeter, the red blood cells, 4,200,000 per cubic millimeter, and the hemoglobin was 7.4 Gm. per 100 c.c.

Urinalyses were all within normal limits. Micro nonprotein nitrogens taken on several occasions ranged from 25 to 40. A blood culture showed no growth. Throat culture revealed the predominant organism to be *Staphylococcus albus*. The serum calcium was 9.5 mg. per 100 ml.; a micro-Hinton was negative.

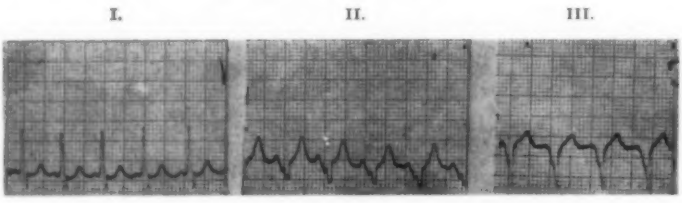


Fig. 4.—Electrocardiogram taken three months after patient was discharged from hospital. Auricular rate, 140; ventricular rate, 140; P-R interval, 0.08 sec.; QRS interval, 0.11 sec.; Q-T, 0.28 sec.; rhythm, sinus tachycardia; electrical axis, right; S-T depressed in $V_2$-$V_3$; T inverted in $V_1$-$V_2$; R-R in $V_1$-$V_2$. Conclusion: Wolff-Parkinson-White syndrome with sinus tachycardia.

The patient was seen at the age of 2 months and at the age of 1 year for follow-up electrocardiograms. Electrocardiographic tracings on both follow-up visits revealed sinus tachycardia and continued evidence of Wolff-Parkinson-White syndrome. (Fig. 4.)

There have been no episodes of cyanosis or respiratory distress. The patient has been clinically well since discharge.

## SUMMARY

This is a case report of a 48-hour-old infant hospitalized because of cyanosis and rapid respiration. Besides the common complications of

paroxysmal tachycardia and congestive failure,[9] there were electrocardiographic evidences of paroxysmal tachycardia and of the Wolff-Parkinson-White syndrome. The congestive failure and paroxysmal tachycardia responded clinically and electrocardiographically to digitalization, the rhythm and rate returned to normal, and the cardiac dilatation subsided, but evidence of the Wolff-Parkinson-White syndrome still persisted on electrocardiograms.

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# HEMATEMESIS

## Report of a Case in an Infant Due to Arterial Bleeding From the Base of the Tongue

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THE occurrence in an infant of severe hematemesis can present a difficult diagnostic problem. Usually, in the differential, we consider blood dyscrasias, pulmonary disease, peptic ulcer, esophageal varices, hemangioma, retropharyngeal abscess, and varices of the tongue.[1, 2]

It is the purpose of this paper to report a case which illustrates (1) an unusual cause of hematemesis in an infant—arterial bleeding from a vessel located at the base of the tongue, and (2) diagnostic and therapeutic difficulties encountered before a correct solution was reached.

### CASE REPORT

A Negro male infant, aged 3 months, was admitted to the Beth-El Hospital with bleeding from the mouth.

The mother stated that she first observed some blood in the nursing bottle during a feeding when the baby was 1 month old. Several hours later the baby vomited a large quantity of blood and was admitted to a local hospital. Efforts to control the hematemesis with transfusions gave only short and temporary relief. Postnasal tamponage resulted in an increased blood flow. Every attempt to locate the site or the cause of the bleeding was met with failure. Repeated nose and throat examinations were negative. Esophagoscopy not only failed to reveal a site of hemorrhage but precipitated a prolonged bleeding episode. A gastrointestinal series was repeated twice without uncovering any clues. The stools were constantly tarry. The urine, platelet count prothrombin time, and vitamin C levels were persistently normal. Finally, based on a clinical impression of peptic ulcer and, also, concerned with the dangers of repeated profuse hemorrhage, an exploratory laparotomy was done. This, too, failed to locate a cause of the unrelieved hematemesis. The infant was then transferred to the Beth-El Hospital after eight weeks of hospitalization.

On admission the patient weighed 8 pounds 13 ounces, 2 ounces above birth weight. He appeared marantic, restless, pale, dehydrated, and frequently assumed a tonic neck reflex position. There was intermittent spasticity of the extremities. A discharging osteomyelitis of the right tibia secondary to a bone marrow transfusion was present. The pharynx was filled and overflowed with fresh blood.

Bone marrow aspiration revealed a compensatory erthroblastosis; hemoglobin (Haden-Hausser) was 48 per cent; red blood cell count 2.1 million; reticulocytes 10 per cent. The white blood cell count, differential smear, bleeding time, coagulation time, and platelet count were normal.

The esophagus roentgenogram and the gastrointestinal roentgenogram were negative.

Supportive treatment with frequent transfusions, careful and adequate feedings, and vitamin and iron medication had little effect other than to keep the infant alive.

Ten weeks after admission, during a repeat esophagoscopy, a pinhead-sized pulsatile bleeding point was discovered for the first time on the right side of the base of the tongue. A

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suture was passed through the tip of the tongue and an electric cautery was applied to the exposed bleeding area.

Bleeding stopped promptly and completely. The infant gained 15 ounces in a week. The hemoglobin rose to 88 per cent and the red blood count to 4.63 million. Three weeks later the patient was discharged in excellent physical condition.

## CONCLUSION

We have presented a case of hematemesis in an infant. Many errors were made before a correct diagnostic and therapeutic solution was reached. The infant's condition became desperate. The cause of the episodes of severe bleeding was finally discovered to be a pinhead-sized pulsatile vessel at the base of the tongue. The area was cauterized and the infant made a rapid recovery.

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# Medical Progress

## RECENT PROGRESS IN POLIOMYELITIS RESEARCH

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THE purpose of this paper is to review some recent developments in poliomyelitis research which are paving the way toward the ultimate control of this disease. The new discoveries or activities include the propagation of poliomyelitis virus in tissue culture, the grouping of strains of poliomyelitis virus into three immunologic types, the development of complement fixation tests, the recognition of viremia, certain quantitative studies, and trials of methods for passive and active immunization of human beings.

### PROPAGATION OF POLIOMYELITIS VIRUS IN TISSUE CULTURE

Enders, Weller, and Robbins[1a, b] reported in 1949 that poliomyelitis virus can be made to multiply in various human embryonic tissues, non-nervous as well as nervous. This represents the most important discovery in the field of poliomyelitis since the virus was first isolated in 1909.

Of even greater importance than the propagation of poliomyelitis virus in cultures of various tissues is the fact that it produces visible changes in the growing cells.[1c] Moreover, these cytopathogenic changes are specifically inhibited by immune serum. These striking discoveries provide a basis for the in vitro isolation and identification of poliomyelitis virus, for its quantitation, and for serologic typing.

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Robbins, Enders, Weller, and Florentino[1d] have shown that virus also grows in tissue cultures of kidney from young children and of adult human uterus. These observations have been confirmed and extended by others. Multiplication of virus has been demonstrated in cultures of adult human testis[2, 3] and of monkey testis and kidney.[1g, 3, 4, 5, 6, 7, 8, 41] The latter tissues have already proved useful in the isolation and typing of strains, and in providing virus which when mixed with adjuvant and inoculated into monkeys gives rise to neutralizing antibody titers comparable to those obtained with infected nervous tissue, and without the danger of allergic encephalitis associated with injections of the latter.[9] Moreover, Enders, Weller, and Robbins[10] have reported that by successive tissue culture passages the pathogenicity of poliomyelitis virus was reduced markedly for the monkey. It may be possible by this approach to attenuate its infectivity, while retaining its immunogenic capacity, for man.

Scherer, Syverton, and Gey[11] have shown recently that cells derived from a human epithelial carcinoma will support the propagation of poliomyelitis virus. This method has the advantage of providing a continuous source of cells which can be grown in perpetuity in the laboratory. Also, the destructive effects of poliomyelitis virus are seen within twelve to ninety-

six hours. The yield of virus is as great or greater than that from cultures of human or monkey tissues. Although the use of these cancer cells may prove superior for the isolation and typing of poliomyelitis virus and other laboratory procedures, it seems doubtful that they would constitute a desirable medium for the production of virus to be incorporated in vaccines.

The application of tissue culture methods, in general, to poliomyelitis means that a relatively simple, inexpensive, and practical test object can now take the place of the cumbersome and expensive monkey which retarded progress in poliomyelitis more than any other single factor. It opens the field to new workers and should soon make possible the creation of clinical diagnostic laboratories for the detection of poliomyelitis infection.

### GROUPING OF POLIOMYELITIS VIRUSES INTO IMMUNOLOGIC TYPES

To approach intelligently the problems of diagnosis, immunity, and epidemiology it is essential to have accurate knowledge of the antigenic variations of poliomyelitis virus. Although reports from several laboratories since 1931 suggested the existence of more than one immunologic type of virus, it was not until twenty years later that the Committee on Typing of The National Foundation for Infantile Paralysis presented the results of a series of well-organized systematic studies of 100 selected strains of poliomyelitis virus.[12] This committee found that the 100 strains fell into three broad immunologic types as follows: Type I (Brunhilde), 85 strains; Type II (Lansing), 12 strains; Type III (Leon), 3 strains. The typing was carried out in monkeys by three methods: (a) by testing resistance of monkeys immunized with prototype viruses; (b) by serum neutralization tests with prototype antisera, and (c) by neutralization of prototype viruses with sera from monkeys immunized with unknown strains combined with adjuvants. The latter method was found especially useful in typing strains of low titer.[13] The results showed good agreement between the three methods regarding the identification of most of the strains studied. Two different virus types were isolated at each of two epidemics and serologic evidence suggests that this is not uncommon. Weller tested strains different from those reported by the Typing Committee. He observed that the distribution of virus types as determined by tissue culture techniques varies somewhat from the above results.[14] The differences are compared in the accompanying table:

| | *Immunologic Type (%)* | | |
|---|---|---|---|
| | I | II | III |
| Monkey (Typing Committee) | 85 | 12 | 3 |
| Tissue culture (Weller) | 60 | 10 | 30 |

More Type III and fewer Type I strains were identified by tissue culture than by monkey tests. It is possible that the Committee's arbitrary method of selection of strains for typing gave a less accurate pattern of distribution than that found by tissue culture. The use of tissue culture techniques has also brought to light a number of strains which are not neutralized by the three known types of immune sera. These strains were isolated from patients diagnosed clinically as poliomyelitis or suspected poliomyelitis. They produced typical cytopathogenic changes in cultures of monkey testicular tissue[15, 16] and of human embryonic tissue[16] but were

not pathogenic[16] or weakly pathogenic for monkeys.[15] In some instances the development of neutralizing antibody was demonstrated in convalescent serum for the virus isolated from the patient. A few of the agents proved to be pathogenic for suckling mice and could therefore be classified as Coxsackie-like viruses, but most were not. It is difficult to categorize these so-called "query viruses" at present. The evidence suggests that some, at least, may be strains of poliomyelitis with an unusual "host range" and different immunologic properties. Future work is bound to throw light on these variants and also on the extent of antigenic and other differences to be found within the three major types. The antigenic variation of poliomyelitis viruses has an obvious bearing on the composition of vaccines. It also serves as the probable explanation for second attacks of the paralytic disease.[17]

### COMPLEMENT FIXATION TESTS

It is striking that within the last three years two glassware tests have been developed for the recognition of poliomyelitis infection—tissue culture and complement fixation (CF) tests. Although others had reported a CF test for poliomyelitis,[18] Casals and Olitsky[19, 20, 21] were the first to devise a reproducible test, which has since been confirmed in several laboratories.[22, 23] The trick which led to their success was the adaptation of the MEFl strain (Type II) to newborn mice. After multiple serial passages, virus was obtained in high titer from the baby mouse brains. From this material a CF antigen was prepared which reacted specifically with sera from animals immunized with Type II virus and from primates convalescent from infection with this virus. A considerable number of sera from recently convalescent patients had significant titers of CF antibody for the Type II antigen in spite of the absence of Type II neutralizing antibodies. These results suggested that CF antibody response in human beings infected with poliomyelitis virus might not always be type specific. Casals, Olitsky, and Sabin[24] proceeded then to establish the fact that patients infected with Type I virus developed CF antibody for Type II antigen. There was no evidence of previous or concurrent infection with Type II virus in these Type I-infected patients. In general, the sera of 67 per cent of eighty-one poliomyelitis patients yielded significant CF antibody titers (1:16 or higher) in contrast to 13 per cent of 127 summer and autumn controls and 3 per cent of thirty-two winter controls. The authors conclude that "the application of these data to the serologic diagnosis of poliomyelitis infection in man will of necessity be limited until information is obtained on the development, persistence, and significance of CF reactions with antigens deriving from Type I and Type III poliomyelitis strains."

That progress has already been made in this direction is indicated by the studies of Svedmyr, Enders and Holloway[25] who prepared antigens in tissue culture with the three types of poliomyelitis viruses. They found that the CF antibody response of immunized or convalescent monkeys was type specific. In human beings, however, infection with one type of virus may give rise to CF antibodies that react also with other types. They suggest that such cross reactions are

caused by the presence of both type specific and group antigens in the poliomyelitis viruses.

Goldblum and Melnick,[26] working with MEFl antigen prepared by the method of Casals and Olitsky, have shown that in contrast to the persistence of Type II *neutralizing* antibody for many years, CF antibody (Type II) tends to fall more rapidly. Thus the presence in serum of both CF and neutralizing antibodies would indicate recent infection; negative CF and positive neutralization, old infection; negative for both, no infection.

Although the development of CF tests for the three known types of poliomyelitis virus infection represents a major achievement, it seems clear that as already mentioned more work must be done on the rise and fall and significance of CF reactions with the three types of antigens before the test can be used as a practical diagnostic tool.

### VIREMIA IN POLIOMYELITIS

Until recently poliomyelitis virus has been found rarely in the blood of human beings.[27, 28] It occurred to Horstmann[29] that viremia might be present during the incubation period and that by the time the disease declares itself it is too late to detect virus in the blood. This concept fits with the already established presence of serum antibody at the onset of illness.[30, 31] Independent studies carried out simultaneously in two different laboratories demonstrated viremia in primates fed virus. Horstmann detected viremia in seven of ten cynomolgus monkeys and in three of four chimpanzees which had been fed poliomyelitis virus four to six days before. Virus was found in the blood from three to seven days before onset of paralysis in the cynomolgus monkeys.[29] Bodian[32] also demonstrated viremia early in the course of infection by the alimentary route. Two of his three chimpanzees had viremia "in the prefebrile period, just before a sharp serum antibody rise (from 0 to 1:1000 in 2 days), and 2 to 5 days before onset of paralysis." Serum antibody titers were 1:1,000 in both animals at onset of paralysis. Bodian reported that gamma globulin apparently prevented viremia and paralysis in three chimpanzees. Two of them excreted virus in the stools and in these animals an antibody response characteristic of active infection, albeit delayed and lower in titer than that of the controls, was demonstrated.

It is significant that this year both of these workers have described the successful carry-over of their observations in experimental animals to naturally infected human beings. Bodian and Paffenbarger[33] detected three strains, all Type I, in the sera of three children, respectively, who had fever either on the day of bleeding or one to two days after, but no signs of subsequent invasion of the central nervous system. One month later the three children had serum neutralizing antibody titers of 1:3,000, 1:1,000, and 1:1,000 against Type I virus. One child possessed in addition a titer of 1:100 against Type II. Horstmann and McCollum[34] isolated virus from the blood of four children in one family. Three of them had characteristic signs and symptoms of abortive poliomyelitis and one was asymptomatic. Throat and rectal swabs from all four yielded virus also. It is important to note that these four isolations of virus from the blood were made in roller

tubes containing cultures of monkey testicular (or kidney) tissue, and that direct inoculation of monkeys with blood failed to yield virus which suggests (1) that only small amounts of virus were present, and (2) that tissue culture may be more sensitive than monkeys for original isolation of virus.

What is the significance of viremia in poliomyelitis? Bodian[35] believes it to be an important feature in pathogenesis. His working hypothesis includes three phases of virus multiplication: (1) in the alimentary tract, (2) in the blood or organs in close relation to the blood stream (lymph nodes, spleen, etc.), and (3) in the nervous system. He believes that virus may invade the latter not only along nerves from the throat and intestine but may also penetrate the central nervous system from the blood stream at a single point. Bodian thinks that the rapid and high level of antibody response is most likely the result of the vascular phase of virus multiplication. Moreover, the finding that barely detectable levels of passive serum antibody can prevent paralysis in cynomolgus monkeys given virus by mouth suggests that paralytic poliomyelitis in man should be readily prevented by levels of serum antibody easily achieved with gamma globulin or with killed virus vaccines.

### QUANTITATIVE STUDIES OF EXPERIMENTAL POLIOMYELITIS AND OF EXCRETION OF VIRUS IN PATIENTS' STOOLS

Sabin and Winsser[36] found a quantitative relationship between the concentration of virus fed to cynomolgus monkeys and the character or severity of the resulting illness. When $10^{-1}$ virus was given in three daily oral doses of 5 ml. each, almost 100 per cent became infected, 60 per cent being paralytic; $10^{-2}$ virus resulted in 60 per cent becoming infected, 24 per cent paralytic; $10^{-3}$ virus, 43 per cent infected, 14 per cent paralytic; only one of eighteen monkeys (6 per cent) became infected with $10^{-4}$ virus, and $10^{-5}$ virus produced neither paralysis nor antibody. When minute amounts ($10^{-4}$) were ingested daily over long periods, 60 per cent developed antibodies at the end of 4½ months, and of the total number of infections, 82 per cent were inapparent. An unexpected finding occurred when fifteen monkeys which had no demonstrable serum antibody after repeated virus ingestion, nevertheless exhibited significant resistance to paralysis. Only 14 per cent became paralyzed although all developed antibody when challenged with a large oral dose of virus. Sabin and Winsser believe that this represents immunity acquired at the portal of entry unassociated with detectable antibody in the serum. It indicates one of the mechanisms by which poorly sanitated populations having a relatively low incidence of paralysis may become immune to poliomyelitis.

Another quantitative study has been carried out which suggests that the amount of virus excreted in the stools of poliomyelitis patients may be related to the severity of illness.[37] The stools of paralytic patients yielded very high titers of virus averaging 1:5,000 (dilution of stool giving the 50 per cent end point in rhesus monkeys inoculated intracerebrally, six animals per dilution). The stools of nonparalytic patients and those with mild transitory weakness, on the other hand, gave titers which with one exception were uniformly much lower,

averaging 1:175, a difference of almost thirtyfold. If this finding can be confirmed, it offers an approach to the study of host factors perhaps in the alimentary tract which foster the multiplication of poliomyelitis virus to high levels associated with paralysis.

### PREVENTION OF POLIOMYELITIS

The ultimate aim of most research in poliomyelitis is to prevent or modify the disease. Important strides have been made recently in the application of the direct approach, namely, passive and active immunization.

*Passive Immunization.* — Hammon, Coriell, and Stokes[38a, b, c] together with Wehrle[38d] have reported the results of three controlled field trials to evaluate the effect of Red Cross gamma globulin in the prevention of paralytic poliomyelitis. This colossal undertaking evokes the admiration of those aware of its complexities. No attempt will be made here to review the work in its entirety but rather to outline the results. Over 27,000 children received gamma globulin in an average intramuscular dose of 0.14 c.c. per pound of body weight; an equal number of controls received gelatin, and over 100,000 children received no injection in three epidemic areas during 1951 and 1952. Unmistakable protection occurred from the second to the fifth weeks, inclusive, after the injections. During this period a total of forty-six paralytic cases occurred in the injected groups—thirty-nine in the gelatin group and seven in the gamma globulin group. This could happen by chance alone less than once in a thousand times. During the first week and after the fifth week the difference was not significant.

Even during the first week following injection, however, *modification* of severity was observed in those who received gamma globulin. Twenty-eight children in both groups became paralyzed within one week of injections; seven of these made a complete recovery within sixty days; six had received gamma globulin, and one, gelatin. Expressed otherwise, six of twelve injected with gamma globulin went on to complete recovery while only one of sixteen in the gelatin group did so. In patients who became paralyzed later than the first week following inoculation, no modification of severity by gamma globulin was observed. No evidence was found to indicate that gelatin had caused localization of paralysis in the inoculated limb. However, the attack rate in Texas during the two weeks after closing the clinics *appeared* higher in those receiving gelatin (0.7 per 1,000) than in those not inoculated (0.3). The authors believe this apparent difference was caused by incomplete reporting in those not inoculated.

The scope of this review does not include indications for the future use of gamma globulin. On the basis of this report, 250 to 2,000 prophylactic injections will have to be given to protect one person for five weeks. In the absence of enough material for mass prophylaxis (or even for the most vulnerable age groups), it seems wise to limit its use to epidemics and in the epidemics, to intimate family or family-like contacts of cases or of suspect cases, and to pregnant women.

*Active Immunization.*—The objective is a safe killed vaccine or a safe attenuated living virus which can be prepared on a large scale and which, when administered to human beings,

will give rise to lasting protection with a minimal risk of untoward reactions. Recent developments indicate progress toward the realization of some of these aims. The propagation of virus by tissue culture methods offers a potential source of large quantities of antigen relatively free of extraneous material. The application of Freund's adjuvant techniques,[39] using active virus combined with adjuvant as the antigen, was shown to enhance antibody formation in monkeys.[40] Salk, Lewis, Youngner, and Bennett[13] confirmed this finding and reported that tissue culture virus inactivated by formalin and combined with adjuvant was antigenic for monkeys.[9] Salk and his associates[41] have transferred this approach to a trial in a limited number of human beings. Vaccines noninfectious for monkeys were prepared with each of the three known immunologic types of virus grown in cultures of monkey testicular or kidney tissues. The injection of these vaccines incorporated in adjuvant resulted in serum antibody formation in human subjects. The levels of antibody appeared comparable to those resulting from natural infection and were shown to persist for at least four and one-half months. The authors emphasize that their results although encouraging should not be interpreted to indicate that a practical vaccine is now available.

It has been suggested that the administration of attenuated living virus, perhaps by mouth, to infants might be a safe and effective way of protecting man against poliomyelitis.[42] Support for this idea is derived from the results of feeding poliomyelitis to chimpanzees. It is known that such feeding is followed by (1) excretion of virus in the stools for some time, (2) emergence of serum neutralizing antibody, and (3) the development of resistance to subsequent feedings of homologous but not of heterologous virus strains.[43, 44, 45] Sabin and Winsser's[36] demonstration of resistance in cynomolgus monkeys with and without detectable serum antibody following repeated ingestion of small doses of virus has an important bearing on this approach.

Koprowski, Jervis, and Norton[46] have already performed a courageous study in man. They fed twenty human volunteers a living Type II strain of virus adapted to cotton rats and characterized by low pathogenicity for monkeys. Although none of the subjects developed signs of illness, most of them acquired "alimentary infection" as shown by excretion of virus in stools. All of the nonimmune volunteers showed a prompt rise in serum antibody. Eleven were refed homologous virus one or more times; in nine no virus appeared in the stools and no significant change in antibody level was observed. In two others, despite respectable antibody titers after the initial feeding, "alimentary infection" was observed on three separate occasions in one individual, and on two occasions in the other.

Another important contribution is that of the group at Cox's laboratory.[47] These investigators successfully adapted a Type II strain of poliomyelitis virus to the chick embryo. After numerous serial passages they found that whereas infectivity of the egg material was augmented for the mouse, it was reduced for the monkey. Furthermore, the chick embryo adapted virus proved to be antigenic in chim-

panzees both after feeding and after intramuscular injection.

In this paper an effort has been made to review only some of the recent accomplishments in this field. It would not be too surprising to discover current investigations or reports which will ultimately prove to be more significant than those discussed here. But the direction now being taken by many laboratories is clear. It also seems likely that, although much has been learned that is encouraging, we will continue to be confronted with the problems of poliomyelitis for some years to come.

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# Psychologic Aspects of Pediatrics

## HOMOSEXUAL BEHAVIOR IN CHILDREN

HARRY BAKWIN, M.D., AND RUTH M. BAKWIN, M.D.
NEW YORK, N. Y.

THE term homosexual in connection with human behavior is generally applied to sexual relations, either overt or psychic, between individuals of the same sex (Kinsey). Homosexuality in this sense is not observed in children, but behavior characteristic of the opposite sex is occasionally encountered. It is not known how many go on to homosexuality in adult life. That some continue in this way is indicated by the fact that the majority of adult homosexuals date the beginning of their unusual behavior back to childhood.

According to Kinsey, homosexual play is frequent in preadolescent boys and is indulged in by 50 per cent or more of the youngsters. The mean age of the first homosexual contact is 9.2 years. Much of the activity is incidental, casual, and without erotic arousal.

Deviant sex behavior is observed more often in boys than in girls, probably because boys who show effeminate behavior are much more likely to excite comment than are girls who dress in boys' clothes, play boys' games, and so on. The condition occurs in white children of all nationalities but is rare in the Negro. It it not related to intelligence, intelligence quotients ranging from moron to superior levels.

Bender and Paster described a group of children with homosexual trends. The manifestations of homosexuality ranged from overt practice to the adoption of behavior patterns characteristic of the other sex. In addition, there were other personality disturbances, presumably related to an inadequate home life. Feelings of inferiority and insecurity were common and expressed themselves in fears and episodes of running away. Feelings of inadequacy and bewilderment were added when the children came to appreciate that they were different from others. A craving for affection and reassurance was a prominent feature and was dependent on a past which was affectionless. Many, however, were unable to show affection or form lasting attachments. Aggressive behavior toward smaller children and submissive behavior toward older playmates were frequent.

Greco and Wright studied ten homosexual boys in a correctional institute. The subjects were extreme in their perversion, fully aware of it, and accepting of it. They were boys who were "patterning their present and future modes of adjustment so as to facilitate the direct gratification

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of their perverse desires." Data were obtained from repeated interviews and from written statements by the subjects. As a control group ten boys who showed no evidence of homosexuality were studied in the same way.

Greco and Wright found that, at some time in their early life, all ten of the affected boys had been in serious need of emotional and social security. An attachment was formed at that time to a man who gave security, understanding, and comfort. When this friend seduced the child, it was accepted because of the deep affection for the individual and the fear of losing his protection. To each child this relationship was at first distasteful and was recognized as immoral. In some, continuation of the perversion led to pleasure and satisfaction, in others it continued only as a means of emotional security. In each instance the homosexual relationship became unimportant after the loss of the cherished friend.

It is the opinion of Greco and Wright that these early experiences conditioned the child to a state of latent homosexuality which crystallized at puberty. When the youth became sexually mature he found some attraction for the other sex. When he again encountered homosexuality it was sometimes rejected at first but, after participation, the pleasure and satisfaction were once more recognized.

Home circumstances, parental attitudes, school adjustment, and intelligence were similar in both groups. The homosexuality was not due to discussing or witnessing homosexual acts, unfortunate experiences with the opposite sex, or identification with the mother or another woman which in these cases seemed to occur only after perversion. Contact with a homosexual man, at the time when affection and security were needed, was the only factor found regularly.

The authors conclude that "when a child's security is threatened either from lack of parental interest and affection, lack of friendships or social recognition, extra precautions should be used in preventing the emotional tie-up between the child and some individual who will exploit him for sexual gratification."

### ETIOLOGY

Homosexual behavior in children has been attributed by Bender and Paster to imitation of an admired homosexual parent of the same sex, the other parent being inadequate; to identification with the parent of the opposite sex, the parent of the same sex being ineffective; or to delayed identification with a parent substitute of the opposite sex following a period of early institutional care.

Few "homosexual" children have had sex experiences, and exposure to homosexual practices is not a common cause. Treatment of the child by the parents as though he were a member of the other sex rarely leads to homosexuality; nevertheless this attitude may encourage a latent tendency in that direction.

Boys are occasionally observed who show behavior characteristic of the opposite sex early in life. They dress up in women's clothes at every opportunity, experiment with cosmetics, and posture like girls. One 5½-year-old boy, in whom this behavior had been observed since he was 3 years old, wanted to be a ballet dancer. In our

experience with these young boys, the family setup has not been unusual. The early appearance of this behavior (in one instance the mother stated "from the very start") suggests an inborn aberration in such cases.

According to Kinsey, all degrees of homosexual activity are observed in adults, from exclusively heterosexual behavior, incidentally homosexual, equally heterosexual and homosexual, predominantly homosexual to exclusively homosexual. He has introduced a rating scale from zero to six, the intensity of the aberration being least at zero (exclusively heterosexual) and greatest at six (exclusively homosexual). He regards this aspect of sex behavior as represented by a continuum with individuals representing every gradation from one extreme to the other. Four per cent of the white male population are exclusively homosexual throughout their adult lives.

Kallmann has studied the occurrence of homosexual behavior in male twins. His findings are shown in Table I.

In the two-egg group of twins, when one twin was predominantly homosexual, the cotwin was found also to be 50 per cent or more homosexual in only 11.5 per cent of the cases. In the one-egg group, when one was predominantly homosexual, the cotwin was similarly aberrant in every instance where the cotwin was available (37 out of 40 cases). The one-egg twins were not only concordant as to the overt practice of their deviant behavior, they also tended to be similar in the part taken in their individual sex activities.

Kallmann's findings strongly support a genetic basis for overt homosexuality, a view originally expressed by Krafft-Ebing. The fact that the two-egg twins, though brought up together in the same homes, failed to show concordance, indicates that environmental factors play a minor role in the etiology of overt homosexualism. It is conceivable, however, that home influences and social factors, i.e., whether such behavior is socially acceptable as in ancient Greece or not, may be more important when the inborn deviation is not so marked.

TABLE I. OVERT HOMOSEXUALITY (KINSEY'S RATING SCALE 3 TO 6) IN THE COTWINS OF 85 MALE HOMOSEXUALS, AGED 18 AND OVER

| ZYGOCITY | NO. OF PAIRS | NO. OF COTWINS WHO WERE HOMOSEXUAL | NO. OF COTWINS NORMALLY HETEROSEXUAL | UNCLASSIFIED |
|---|---|---|---|---|
| One-egg | 40 | 37 | 0 | 3 |
| Two-egg | 45 | 3 | 23* | 19† |

*Includes 7 individuals who had incidental homosexual experience and 1 who was predominantly heterosexual but had more than incidental homosexual experience.
†Includes 14 females and 5 males who were deceased or otherwise unavailable.

In discussing the unreliability of measurements of the estrogenic:androgenic ratio, Wilkins states: "Unfortunately abnormal estrogenic:androgenic ratios have been interpreted as accounting for homosexuality and other perverse behavior on a hormonal basis. It is more probable that when there are no anatomic abnormalities of sex development, such behavior disorders are of psychogenic rather than hormonal origin."

### MANAGEMENT

The first step is a detailed review of the home situation with special

attention to the attitudes of the parents toward one another and toward the child. The dominating mother needs curbing, the passive father needs encouragement to take a more active part in his children's lives. The youngster should be encouraged in behavior characteristic of his sex. Coercion, teasing, and shaming are ineffective and even harmful. Confusions about sex should be clarified and explanations given in terms which the particular child can understand.

Homosexual trends in the adolescent must be approached with care and understanding and are to be regarded as a medical rather than a moral problem. The youth should be removed from the environment of homosexuals. Life should be made interesting with plenty of physical activity and little time for daydreams. Direct and intelligent discussion will often clear up uncertainties and guilt feelings. The youth should be assured that he is in no way physically different from other people and that he is capable of marriage and of having children in normal fashion. Social contacts should be encouraged. Children of the other sex should not be forced on him but he should have ample opportunity to meet them.

Bender and Paster were unable to influence children with homosexual trends which had developed in boarding homes after a period of neglect during early childhood. They classify these children as psychopathic personalities.

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# Comments on Current Literature

## INFECTION IN THE NEWBORN BABY

"INFECTION in the Newborn Baby" was chosen by Alan Monerieff, Nuffield Professor of Child Health, University of London, and Physician, Hospital for Sick Children, Great Ormond Street, London, as his subject for the Charles West Commemoration Lecture. This lecture was delivered in London on Nov. 11, 1952, before the Royal College of Physicians, and was published in the *British Medical Journal*, issue of Jan. 3, 1953.[1]

The lecture is outstanding not only because of the wealth of clinical material included in the text, but also because it constitutes a thoughtful record of the reactions of an experienced clinician to the everyday problems which are encountered by the average physician who deals with newborn infants. In recalling the important role played by Dr. Charles West, a great obstetrician, in the development of pediatrics in Britain, Monerieff refers to West's report describing conditions during the last decade of the eighteenth century. West found that in the Dublin Lying-In Hospital at this time every sixth newborn infant died within a fortnight. As a result of elementary hygienic precautions, especially "efficient ventilation of the hospital," the mortality rate had fallen by 1833 from one in six to one in 58.5. From these experiences stemmed West's interest in the sick child and his energetic agitation for the provision of properly conducted hospital facilities both in obstetrical services and in pediatrics. These efforts resulted ultimately in the establishment of the Hospital for Sick Children, Great Ormond Street, London.

Monerieff emphasizes that infection in the newborn infant is still a serious problem, and refers to the comparatively recent figures compiled by Macgregor[2] (1946, Edinburgh) who found that infection was the cause of neonatal death in 190 of 618 infants, a percentage of 30.7. In this reported series, infection was the commonest single cause of neonatal death, and was responsible for two out of three deaths after the third day of life.

The great difficulty encountered in recognizing sepsis as a clinical syndrome in the newborn infant is reflected by figures reported from the Royal Maternity Hospital, Glasgow.[3] This report states that during the period 1939 to 1943, infection was shown by post-mortem examination and study to be the cause of 15.4 per cent of the total deaths within the first three days of life, whereas on the basis of clinical diagnosis alone, only 3.5 per cent of the deaths was recorded as due to infection. In a careful analysis of the reasons for this discrepancy between clinical and post-mortem diagnosis, the lecturer concludes that there are two fundamental difficulties involved in the failure to recognize neonatal infection: first, the traditional belief that newborn infants are not susceptible to infection, and second, the hesitancy to accept a diagnosis of infection in the absence of fever. Monerieff presents data which indicate forcefully that very often overwhelming infection in the newborn baby may be unaccompanied by significant temperature elevation. In this connection Monerieff quotes from Spence,[4] who made the following generalization: "A newborn infant who becomes abnormally drowsy and refuses its feeds, and is not suffering from cerebral hemorrhage should be suspected of

an acute neonatal infection," and the lecturer adds to this statement: "Any disturbance in the newborn baby after the first few days of life should be regarded as due to infection until proved otherwise."

Moncrieff classifies infections in the newborn infant into three categories, namely, those acquired before birth, during the process of birth, and after birth. In addition to the intrauterine infections which are blood-borne to the fetus, he emphasizes the possible role of inhalation of infected material, referring particularly to a report by White[5] who states that 69 of 360 infants, stillborn or dying during the neonatal period, had aspirated appreciable quantities of particulate amniotic debris. Stress is laid therefore on the need for carrying out a gentle hygiene of the mouth and nasopharynx.

A brief description is presented which covers the main features characterizing infections acquired after birth. Infection gains entrance by way of the mucous membranes of the respiratory tract, by way of the eyes, the skin, the alimentary tract, or the umbilicus. The site of invasion is considered the "primary focus." The secondary stage of generalization usually presents a difficult diagnostic problem especially if the "primary focus" has not been apparent. Moncrieff describes the generalizing sepsis as follows: "Fever . . . may not be obvious. The gain in weight ceases, the child refuses to suck and easily tires; vomiting and diarrhea may take place; the pulse and respirations become rapid and irregular, and there develops an ominous grey look about the child, who becomes dehydrated and inert." The third phase is one of pyemia characterized by skin abscesses or abscesses in the liver, kidney, lungs, bones, et cetera. This general picture of progressive sepsis may result from infection by various microorganisms. To a considerable extent early diagnosis and identification of the particular organism determine prognosis.

Treatment and prevention are discussed at some length by the lecturer, emphasizing the great importance of prevention, and that the personal factor in care of the newborn infant is paramount. A high standard of personal hygiene must be maintained scrupulously by all concerned with the care of the newborn child.

As a final word, Moncrieff points out that efforts in the control of infections among newborn infants and in prevention of neonatal sepsis are especially rewarding. Babies saved from neonatal sepsis will be unlikely to have permanent damage, as compared, for example, with those suffering from rhesus incompatibility, cerebral trauma, or respiratory failure. It is particularly relevant that the clinician have a high degree of suspicion so that any newborn infant who is not doing well may have the benefit of the doubt so far as sepsis is concerned.

RUSSELL J. BLATTNER

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# News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Philadelphia, Pa., May 1, 2, and 3, 1953.

Dr. Joseph Allison, Murphy Army Hospital, Waltham, Mass.

Dr. Herman Weatherby Anderson, 3601 Norfolk Rd., Ft. Worth, Texas.

Dr. Richard B. Anderson, 702 S. Prospect Ave., Madison, Wis.

Dr. Mary Daly Bain, 15 Sunset Ave., Methuen, Mass.

Dr. William P. Barba, II, 5919 Greene St., Philadelphia, Pa.

Dr. Samuel Baum, 219 Lexington Ave., Passaic, N. J.

Dr. Clifton Rowland Brooks, 269 E. Main St., Newark, Del.

Dr. David Bruser, 1305 Bancroft Ave., San Leandro, Calif.

Dr. S. Farnum Coffin, 29 Edgehill Rd., Brookline, Mass.

Dr. Frank Cohen, 712 S. Henderson, Fort Worth 4, Texas.

Dr. Harold L. Connor, 515 Market St., San Francisco, Calif.

Dr. Lewis L. Coriell, Municipal Hospital, Camden, N. J.

Dr. Harry Duffield Cox, Waterview Pharmacy Bldg., Portsmouth, Va.

Dr. Charles H. Crothers, Grove Hill Clinic, New Britain, Conn.

Dr. William Miller Crowell, McLean Hospital, Waverly, Mass.

Dr. Bernard M. Curtis, 1259 Wantagh Ave., Wantagh, L. I., N. Y.

Dr. Garrett E. Deane, 5 Tanglewood Rd., Catonsville 28, Md.

Dr. Samuel de Lange, 239 Central Park West, New York, N. Y.

Dr. Richard Louis Dreifuss, 67-38 108th St., Forest Hills, L. I., N. Y.

Dr. L. L. Eldredge, Jr., 215 Main St., Hingham, Mass.

Dr. Bettina Meyerhof Emerson, 371 Lowell Ave., Newtonville 60, Mass.

Dr. Hobart T. Feldman, 821 Linden St., Allentown, Pa.

Dr. John Sherwood Fifer, 701 E. Broward Blvd., Ft. Lauderdale, Fla.

Dr. Eugene Martin Frame, 2720 Park St., Jacksonville, Fla.

Dr. Robert Gregory Frazier, 10th General Dispensary, APO 757, c/o PM, New York, N. Y.

Dr. Margaret Joan Giannini, 930 Grand Concourse, New York, N. Y.

Dr. Harold J. Greenblatt, 99 W. Main St., New Britain, Conn.

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Dr. Gerard N. Izzo, 125 Hendrix St., Brooklyn 7, N. Y.

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Dr. Joseph Edward Kalbacher, 131 Eglecroft Rd., Westfield, N. J.

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Dr. Sidney Kibrick, 109 Peterborough St., Boston 15, Mass.

Dr. William Robert Kueffner, 1275 Post Rd., Fairfield, Conn.

Dr. Hans W. Kunz, 44 Midland Ave., Bronxville, N. Y.

Dr. Charles Hertzler Kurtz, 37 W. Orange St., Lancaster, Pa.

Dr. William Edward Laupus, The Lynn Clinic, 2900 S. Fort St., Detroit 25, Mich.

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Dr. Olive Emma Pitkin, c/o Dr. Igor Tamm, The Rockefeller Inst. Hosp., 66th St. & York Ave., New York, N. Y.

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Dr. Kenneth Dyer Rogers, Univ. of Pittsburgh Grad. Sch. of Pub. Health, Pittsburgh 13, Pa.

Dr. Max Leslie Rohrer, 21871 Lake Shore Blvd., Euclid 23, Ohio,

Dr. Morton Rosenberg, 1st Lt., 1100 Med. Group, Hq. Comd., U.S.A.F., Bolling AFB, Washington, D. C.

Dr. Philip Rosenberg, 3447 Vista St., Philadelphia 36, Pa.

Dr. Robert Otto Roth, P. O. Box 685, McKenney, Va.

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Dr. George Sato, 2500th Med. Gp., Mitchel AFB, New York.

Dr. William Frederic Schnitzker, Walter Reed Army Hospital, Washington 12, D. C.

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Dr. Edward A. Smith, Jr., 2127 Vallejo St., San Francisco, Calif.

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Dr. William Price Spencer, 5901 Patterson Ave., Richmond 26, Va.

Dr. Charles Edward Stepan, 700 N. Michigan Ave., Chicago, Ill.

Dr. Fred Leslie Stricker, Officers Mail Service, Fitzsimons Army Hosp., Denver 8, Colo.

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Dr. Paul F. Wehrle, 639 Morrison Dr., Pittsburgh 16, Pa.

Dr. Marvin Lee Weil, Children's Hospital, Cincinnati, Ohio.

Dr. Coleman M. Whitlock, Jr., 28 E. Marsh St., Concord, N. C.

Dr. Mark Allan Whitman, 522 W. Hortter St., Philadelphia 19, Pa.

Dr. James Sabey Winn, 51 Livingston Ave., New Brunswick, N. J.

Dr. Richard Atlee Young, 318 N. Potomac St., Hagerstown, Md.

The next oral examination will be held in Miami, Fla., on Oct. 9, 10, and 11, 1953.

The following have been certified in the subspecialty of Pediatric Allergy at the examination at Chicago, Ill., April 28, 1953.

Dr. Percy Hall Jennings, Jr., Berkeley Pediatric Group, 1650 Walnut St., Berkeley, Calif.

Dr. Maurice Kaufman, 180 Market St., Lexington, Ky.

Dr. Carroll M. Pounders, 504 Osler Bldg., 1220 N. Walker Ave., Oklahoma City, Okla.

Dr. Walker L. Rucks, 1073 Madison Ave., Memphis, Tenn.

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Dr. Leona Baumgartner, Assistant Commissioner of the New York City Department of Health in charge of maternal and child health services, has resigned to become Ex-

ecutive Director of the New York Foundation. Dr. Harold Jacobziner, Director of the Department's Bureau of Child Health, will succeed Dr. Baumgartner as Assistant Health Commissioner.

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Dr. Glidden L. Brooks, of Pittsburgh, Associate Professor of Pediatries, University of Pittsburgh School of Medicine, has been appointed full-time Medical Director for United Cerebral Palsy whose headquarters are in New York.

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At the 65th Annual Meeting of the **American Pediatric Society** at Atlantic City, May 6 to 8, the following officers were elected for 1953-1954:

President: Rustin McIntosh
Vice President: Wilburt C. Davison
Secretary-Treasurer: Aims C. McGuinness
Recorder-Editor: Stewart H. Clifford
Member of the Council (7 years): John A. Anderson

The following were elected to membership:
Dr. Neva M. Abelson, Philadelphia.
Dr. Janet S. Baldwin, New York.
Dr. William Berenberg, Boston.
Dr. A. L. Chute, Toronto.
Dr. Clifford G. Grulee, Jr., New Orleans.
Dr. Janet Hardy, Baltimore.
Dr. Chris P. Katsampes, Rochester.
Dr. John D. Keith, Toronto.
Dr. John A. Lichty, Denver.
Dr. Edmund R. McCluskey, Pittsburgh.
Dr. Robert J. McKay, Burlington.
Dr. Lawrence B. Slobody, New York.
Dr. Alexander J. Steigman, Louisville.
Dr. Lewis Thomas, Minneapolis.
Dr. Richard Wagner, Boston.

At the Annual Meeting of the **National Board of Medical Examiners** on May 3, 1953, Dr. A. Ashley Weech of Cincinnati was elected to membership to succeed Dr. Borden S. Veeder who has served two terms of six years. Dr. Weech automatically becomes chairman of the Pediatric Test Committee. This committee now consists of the chairman, Dr. Henry Barnett, Dr. James Baty, Dr. James Hughes, Dr. Milton Rappaport, and Dr. Francis Schwentker.

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The **Society for Pediatric Research** held its 23rd annual meeting in Atlantic City, New Jersey on May 4 to 6, 1953. Dr. Robert Ward, New York, presided. The following officers were elected for 1954:

President: Dr. Harold Harrison, Baltimore.

Vice President: Dr. Russell Blattner, Houston.

Secretary-Treasurer: Dr. Sydney S. Gellis, Boston.

Members of Council: Dr. Charles Lowe, Buffalo, Dr. C. Henry Kempe, San Francisco.

Dr. Rene Dubos of New York City was the guest speaker at the banquet.

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The **Seventh International Pediatric Congress** will be held at National Capitol, Havana, Cuba, October 12 to 17, inclusive. For reservations and further details write to Organizing Committee of International Pediatric Congress, Hospital Mercedes, Vedado, Havana, or to Gomez Tours, Havana, Cuba.

# Book Reviews

**Teach Your Child to Read.** Mary Aline Cox, New York, 1953, Exposition Press, 35 pages. Price $2.00.

That reading difficulties in children have increased since the "sight method" of teaching reading has come into common use in the schools is well known. Further, that behavior problems develop in children due to their failure to make normal progress as a result of reading difficulties is a common experience in pediatric practice. Practically every pediatrician of a few years' experience encounters children of superior intelligence who fail to progress in school due to reading difficulties. The only remedy has been to find a remedial reading teacher who teaches by the good old alphabetical method used by past generations. Unfortunately it is difficult to find such teachers even in the larger cities. Miss Cox, an elementary teacher for many years in the schools of Sacramento, California, has devised a remedial teaching method with which she states she has never had a failure. She further states that any fairly intelligent parent by following her method which is described in this book can teach a child with reading difficulties to read. The text is short, direct, and easy to understand. She does not go into the theories of why reading difficulties develop, but simply presents and describes her own method which she has taught parents to use. The text and method should be of particular value to parents in the smaller cities and communities where experienced teachers in remedial reading are not available.

**Food for Life.** Edited by Ralph W. Gerard, Ph.D., M.D., Chicago, 1952, University of Chicago Press, 306 pages. Price $4.75.

This unusual discussion of food and metabolism, edited by the professor of physiology at the University of Illinois, is one of the most interesting books the reviewer has run across in a long time. It is quite unlike the usual text on nutrition, and there are no tables of food values, diet lists, and the like. Rather Dr. Gerard and a group of five authorities in the field—Block of New York Medical College, Jolliffe of the Bureau of Nutrition of New York City, McCay and Smith of Cornell at Ithaca, and Soskin of Northwestern—have presented a most readable, broad discussion of foods and how they are utilized in the body. While each chapter has been the particular responsibility of some one of the group, there is an evenness in the discussions and a continuity which reflects a remarkable accomplishment on the part of the editor. Starting in with a discussion of the basic questions of nutrition, the nutrient materials in food are discussed; next the preparation of foods from mouth to cell and the processing that takes place in the various organs and cells. Chapters follow on the enzymes, and regulation of cell metabolism. Finally a discussion of the foods of animals and man and the improvement of human nutrition.

This brief listing of the contents in no way describes the clear and understandable way in which the most complicated metabolic problems and processes are presented. Not the least attractive part of the book are the unusual clever graphic drawings illustrating the text. Many of these would be of great value to the teacher. While perhaps the material presented in the book is familiar to the recent graduate, we are certain that much of it is unfamiliar to the practitioner of a few years' standing. He will find the text a liberal postgraduate education, as well as interesting reading. It cannot be too highly recommended as a course in the "basic sciences" of nutrition.

# Editor's Column

## ATHLETIC COMPETITION FOR CHILDREN

PHYSICAL exercise is recognized as essential for the health and development of the growing child. Over the years the more formalized gymnasium work and calisthenics for the school child has largely been replaced by organized games and sports. Unfortunately, like everything else that change brings about, the development of the sports program has created new problems. Many interested in education have become concerned over certain tendencies in connection with competitive sports that started with the college, extended to the preparatory school, and in turn to the elementary school. We are chiefly interested with this last group so far as the child's health and development are concerned. Unfortunately, judgment as to the effects of the sports program, or as to the desirability of a specific game, is based on opinion rather than factual knowledge.

Recently a report on "Desirable Athletic Competition for Children" was issued by a joint committee made up of representatives of the Association for Health, Physical Education, and Recreation, the Society of State Directors of Health, Physical Education, and Recreation, the Council of State Consultants in Elementary Education, and the Department of Elementary School Principals of the NEA. The report deals with athletic competition for children of elementary and junior high school age, and emphasizes its value as an educational experience and as an aspect of community life. The first part of the report presents the recommendations of the committee and with these in general no one can quarrel. They include a broad program for all boys and girls, intramural competition, no interschool competition of a varsity pattern for children below the ninth grade, and the avoidance of "high pressure practices." By this term is meant highly organized competition in the form of leagues or championships, overemphasis by the press, the selection of all-star teams, tournaments, night games, commercial promotions, and similar matters which tend to turn the objective of a program of sports and exercise for all into a winning school team. With these recommendations the pediatricians will wholeheartedly agree. It is just common sense. The definite statement is made in the recommendations that boxing at all levels, and tackle football below the ninth grade are considered undesirable under any conditions. Many will disagree with this statement.

Part two of the report contains the "findings" upon which, it is stated, the recommendations are based. This consists of what is termed a study of physiological factors, psychological factors, safety factors, and economic factors. In reality the so-called "studies" are nothing more than an expression of opinion and are not factual. Moreover, the tables and discussions emphasize the differences of opinion that exist rather than a unanimity of opinion. Thus while we can agree with the recommendations as a whole, it is difficult to see how they are based on the findings of the studies.

Questionnaires were sent to a group of 424 pediatricians, cardiologists, orthopedic surgeons, physiologists, and general practitioners, asking their opinion on certain questions. Two hundred twenty or 52 per cent replied. We note that seventy-eight of 109 pediatricians (71 per cent) who were sent questionnaires replied, which reflects their interest in the subject. Six questions were asked as to certain factors which could be considered valid in determining the kind and extent of athletic activities for youths aged 12 to 15 years (upper grade or junior high school ages). Of the questions asked, only the "likelihood for carry-over of activity past the stage of healthful fatigue to harmful exhaustion" was considered a valid factor by more than half (61 per cent). This was considered as a valid factor by 74 per cent of the pediatricians. Vulnerability of joint injury and special hazard in connection with fracture of the epiphyseal area came next with 45 and 47 per cent, respectively. However, we note that these were considered valid factors by 70 per cent of the orthopedists who replied. Thus there is a wide difference of opinion not only as a whole but as expressed by the different groups in the light of their experience.

A second question was as to whether eleven listed competitive games should be prohibited, approved for intramural competition, or approved for interschool competition. In the opinion of 104 of the 220, or approximately one-half, football should be prohibited. Soccer came next with about one-fourth disapproving. There were only two objections, less than one-half per cent, to baseball, softball, and swimming. Twenty-eight were of the opinion that track and field competition should be prohibited. Turning to the other extreme, approval for interschool competition, we note that baseball was approved by eighty-five (39 per cent), track and field by fifty-four. Only twenty-two (10 per cent) approved of interscholastic football at this age. Roughly all eleven sports received a 50 per cent approval for intramural competition. Opinions of more importance would have been obtained had the questionnaire been sent to a representative group of public and private school physicians.

When we turn to the "psychological study" even greater variation in opinion exists. A group of thirty-one psychiatrists, psychologists, and experts in child growth were sent a set of eight questions, and twenty replied. The committee obviously found it impossible to tabulate the answers and so some ten pages of the report are given over to excerpts from the answers to the questions. After reading them we are at a loss to sum up just what it all amounts to.

The report is a laudable attempt to formulate opinion and to scrutinize athletic competition for the elementary school child. While the report presents many recommendations with which the pediatrician will agree, the findings of the study, upon which it is stated the recommendations are based, are quite unsatisfactory to be considered as a basis for some of the recommendations.

For example, a yes or no opinion as to a specific sport as football can only be made if a number of qualifications are taken into consideration. Are the players evenly matched as by some method as the California A.B.C. system? Is the playing field graded with a good turf, or is it a rough lot dangerous in itself? Is there competent

coaching and supervision for all squads? Does each child have good equipment in the way of helmet, shoes, and properly padded sweater and pants? (Incidentally, we might add that a complete football outfit costs about $50 per child which makes it a prohibitive sport for many.) Very few schools can in all probability meet such requirements and tackle football without them is best prohibited. On the other hand, we know of schools that meet these requirements and hence the sport might well be approved. While track and field sports were more generally approved, there should be definite qualifications before a categorical approval or disapproval. The longer dash events and distance runs are not satisfactory events for children at this age.

Most of the recommendations as those having to do with "high pressure" methods are most sane and needed. The approval or disapproval of individual sports as to their prohibition, or as satisfactory for intramural and interschool competition, requires much further study than is found in the report before sound recommendations can be made.

## AN APOLOGY TO TEXAS

THE editor wishes to apologize for an erroneous statement in the editorial on "Snake Bites" in the May issue. The statement was made that all the poisonous snakes found in the United States belong to the family Crotalidae, or "pit vipers." This was based on statements made in some pamphlets on snakes and snake poisoning read in preparing the editorial. The editor, not being a herpetologist, accepted the statements at face value.

Our attention has been called by some Texas friends to the fact that Texas is the home of a poisonous snake of the Elapidae species related to the cobra group. It is the "Texas coral snake" found in a number of counties in southeastern Texas. The coral snake is a slender, brilliantly colored serpent usually under 2½ feet in length. It is not aggressive and the danger lies in its being mistaken for several harmless snakes which closely resemble it in size and coloring. Little is known of the venom which is apparently neurotoxic. Just to add to our discomfiture there is also an "Arizona coral snake" which differs from the Texas variety by having a black head. It is found in Arizona and southern Utah and El Paso County, Texas. It is stated that there is no case record of a human being having been bitten by the Arizona variety.

We might try and crawl out of our error by quoting the definition of the United States as consisting of "47 states and Texas," but we feel honor should go where honor is due. So we prefer to apologize to our Texas friends for our error, and give credit to that great state for another unique phenomenon in its natural resources.

Dr. Kaliski of San Antonio kindly sent us Bulletin No. 31, published in February of this year by the Texas Game and Fish Commission, Austin, Texas, entitled *The Poisonous Snakes of Texas and the First Aid Treatment of Their Bites.* It is by far the best discussion of snakes and snake bite treatment we have seen. Right in the middle of the booklet is a beautiful double-page colored illustration of the Texas coral snake. Shame on us.